WEST Search History

09/776,479

DATE: Wednesday, September 17, 2003

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=ADJ		
L16	L13 and (treatment or treating or treat or prevent or prevention or preventing)	190	L16
L15	L13 and (treatment of treating or treat or prevent or prevention or preventing)	190	L15
L14	L13 and (non-responder or non-responsive)	7	L14
L13	L12 and (hyporesponsive or hypo-responsive or refractory)	190	L13
L12	L8 and phosphorothioate	389	L12
L11	L10 and phosphorothioate	14	L11
L10	L9 and modified backbone	14	L10
L9	L8 and immunostimulatory	96	L9
L8	asthma adj5 allergy and (cpg or nucleic acid)	1093	L8
L7	L6 and (asthma or allergy or cpg or nucleic acid)	13	L7
L6	l1 or l4 or L5	20	L6
L5	fouron-yves.in.	11	L5
L4	petersen-deanna-m.in.	5	L4
L3	peterson-deanna.in.	0	L3
L2	peterson-deanna-m.in.	0	L2
L1	bratzler-robert-l.in.	10	L1

END OF SEARCH HISTORY

Welcome to STN International! Enter x:x

LOGINID:ssspta1813nxm

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	Feb 24	PCTGEN now available on STN
NEWS 4	Feb 24	TEMA now available on STN
NEWS 5	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 6	Feb 26	PCTFULL now contains images
NEWS 7	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 8	Mar 24	PATDPAFULL now available on STN
NEWS 9	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 10	Apr 11	Display formats in DGENE enhanced
NEWS 11	Apr 14	MEDLINE Reload
NEWS 12	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 13	SEP 09	CA/CAplus records now contain indexing from 1907 to the present
NEWS 14	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 15	Apr 28	RDISCLOSURE now available on STN
NEWS 16	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 17	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 18	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 19	May 19	Simultaneous left and right truncation added to WSCA
NEWS 20	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation
NEWS 21	Jun 06	Simultaneous left and right truncation added to CBNB
NEWS 22	Jun 06	PASCAL enhanced with additional data
NEWS 23	Jun 20	2003 edition of the FSTA Thesaurus is now available
NEWS 24	Jun 25	HSDB has been reloaded
NEWS 25	Jul 16	Data from 1960-1976 added to RDISCLOSURE
NEWS 26	Jul 21	Identification of STN records implemented
NEWS 27	Jul 21	Polymer class term count added to REGISTRY
NEWS 28	Jul 22	INPADOC: Basic index (/BI) enhanced; Simultaneous Left and Right Truncation available
NEWS 29	AUG 05	New pricing for EUROPATFULL and PCTFULL effective August 1, 2003
NEWS 30	AUG 13	Field Availability (/FA) field enhanced in BEILSTEIN
NEWS 31	AUG 15	PATDPAFULL: one FREE connect hour, per account, in September 2003
NEWS 32	AUG 15	PCTGEN: one FREE connect hour, per account, in September 2003
NEWS 33	AUG 15	RDISCLOSURE: one FREE connect hour, per account, in September 2003
NEWS 34	AUG 15	TEMA: one FREE connect hour, per account, in September 2003
NEWS 35	AUG 18	Data available for download as a PDF in RDISCLOSURE
NEWS 36	AUG 18	Simultaneous left and right truncation added to PASCAL
NEWS 37	AUG 18	FROSTI and KOSMET enhanced with Simultaneous Left and Right Truncation
NEWS 38	AUG 18	Simultaneous left and right truncation added to ANABSTR

```
 NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 07:59:41 ON 17 SEP 2003

=> file biosis medline agricola embase caba wpids  japio biotechds lifesci caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.63       0.63

FILE 'BIOSIS' ENTERED AT 08:01:24 ON 17 SEP 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'MEDLINE' ENTERED AT 08:01:24 ON 17 SEP 2003

FILE 'AGRICOLA' ENTERED AT 08:01:24 ON 17 SEP 2003

FILE 'EMBASE' ENTERED AT 08:01:24 ON 17 SEP 2003
COPYRIGHT (C) 2003 Elsevier Science B.V.  All rights reserved.

FILE 'CABA' ENTERED AT 08:01:24 ON 17 SEP 2003
COPYRIGHT (C) 2003 CAB INTERNATIONAL (CABI)

FILE 'WPIDS' ENTERED AT 08:01:24 ON 17 SEP 2003
COPYRIGHT (C) 2003 THOMSON DERWENT

FILE 'JAPIO' ENTERED AT 08:01:24 ON 17 SEP 2003
COPYRIGHT (C) 2003 Japanese Patent Office (JPO)- JAPIO

FILE 'BIOTECHDS' ENTERED AT 08:01:24 ON 17 SEP 2003
COPYRIGHT (C) 2003 THOMSON DERWENT AND INSTITUTE FOR SCIENTIFIC INFORMATION

FILE 'LIFESCI' ENTERED AT 08:01:24 ON 17 SEP 2003
COPYRIGHT (C) 2003 Cambridge Scientific Abstracts (CSA)


FILE 'CAPLUS' ENTERED AT 08:01:24 ON 17 SEP 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

=> e bratzler robert l/au
E1            2     BRATZLER R/AU
E2           25     BRATZLER R L/AU
E3           14 --> BRATZLER ROBERT L/AU
```

```
E4          15      BRATZLER U/AU
E5           1      BRATZLER UWE/AU
E6           1      BRATZSLAVSKAYA O I/AU
E7           4      BRAU/AU
E8          55      BRAU A/AU
E9           3      BRAU A C S/AU
E10          1      BRAU AGADE E/AU
E11          1      BRAU AGAUDE E/AU
E12         17      BRAU AGUADE E/AU

=> s e1-e3
L1          41 ("BRATZLER R"/AU OR "BRATZLER R L"/AU OR "BRATZLER ROBERT L"/AU)


=> e petersen deanna m/au
E1           3      PETERSEN DAVID A/AU
E2           4      PETERSEN DAVID M/AU
E3           7 --> PETERSEN DEANNA M/AU
E4           1      PETERSEN DEBBIE/AU
E5           1      PETERSEN DEBORAH J/AU
E6           2      PETERSEN DEBORAH W/AU
E7           3      PETERSEN DEBORAH WISSINK/AU
E8          20      PETERSEN DEN BESTEN A/AU
E9           2      PETERSEN DEN BESTEN ANNELIEN/AU
E10         12      PETERSEN DENISE/AU
E11          1      PETERSEN DENISE M/AU
E12          2      PETERSEN DENNIS E/AU

=> s e3
L2           7 "PETERSEN DEANNA M"/AU

=> e fouron yves/au
E1          17      FOURON Y/AU
E2           1      FOURON Y M F/AU
E3          13 --> FOURON YVES/AU
E4           1      FOURONIE A/AU
E5           9      FOUROT BAUZON M/AU
E6           2      FOUROT H/AU
E7           6      FOUROT J/AU
E8           5      FOUROT M/AU
E9           1      FOUROT Y/AU
E10          3      FOUROUCLAS N/AU
E11          1      FOUROUET J L/AU
E12          1      FOUROUET J P/AU

=> s e1-e3
L3          31 ("FOURON Y"/AU OR "FOURON Y M F"/AU OR "FOURON YVES"/AU)

=> s l1-l3
L4          73 (L1 OR L2 OR L3)

=> s l4 and (asthma or allergic or allergy)
L5           5 L4 AND (ASTHMA OR ALLERGIC OR ALLERGY)

=> s l5 and cpg
L6           4 L5 AND CPG

=> d bib ab 1-4

L6   ANSWER 1 OF 4  WPIDS  COPYRIGHT 2003 THOMSON DERWENT on STN
AN   2003-275279 [27]   WPIDS
DNC  C2003-072415
TI   Treatment of a subject having, or at risk of developing cancer, involves
```

the use of an immunostimulatory nucleic acid having a modified backbone in combination with a cancer medicament.

DC B05

IN **BRATZLER, R L**; PETERSEN, D M

PA (BRAT-I) BRATZLER R L; (PETE-I) PETERSEN D M

CYC 1

PI US 2002156033 A1 20021024 (200327)* 32p

ADT US 2002156033 A1 Provisional US 2000-187214P 20000303, US 2001-800266 20010305

PRAI US 2000-187214P 20000303; US 2001-800266 20010305

AB US2002156033 A UPAB: 20030429

NOVELTY - Treatment (T1) of a subject having cancer involves administering an immunostimulatory nucleic acid (1) having modified backbone and a cancer medicament (M1) selected from chemotherapeutic agent, immunotherapeutic agent, cancer vaccine or hormone therapy. The poly-G nucleic acid is not conjugated to (M1) and is free of **CpG** and T-rich motif.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) Treatment (T3) of a subject having or at risk of developing cancer involving administering an immunostimulatory nucleic acid selected from **CpG** nucleic acid or a non-**CpG** nucleic acid (where the nucleic acid has a phosphorothioate modified backbone) and a cancer medicament such as hormone therapy (HT); and

(2) A device for delivering immunostimulatory nucleic acid to a subject receiving an intravenous injection, comprising an intravenous device (D1) selected from a bag or a tube and the nucleic acid, where the nucleic acid is coated on an internal surface of (D1) or is embedded within (D1).

ACTIVITY - Cytostatic; Fungicide; Antibacterial; Antiparasitic; Virucide; Antiallergic; Antianemic; Hemostatic.

MECHANISM OF ACTION - Cell growth inhibitor.

USE - The composition is for the treatment of cancer (e.g. bone cancer, brain and CNS cancer, connective tissue cancer, esophageal cancer, eye cancer, Hodgkin's lymphoma, larynx cancer, oral cavity cancer, skin cancer, and testicular cancer), and for preventing **allergic** responses in those receiving blood transfusions (all claimed). It is also useful for the treatment of fungal, bacterial, parasitic and viral infections.

ADVANTAGE - The combination of the immunostimulatory nucleic acids and the cancer medicament is synergistic. The combination allows for the administration of higher doses of cancer medicaments without as many side effects, and allows for the administration of lower, sub-therapeutic doses of either compound, but with higher efficacy than would otherwise be achieved using such low doses. The immunostimulatory nucleic acids function by enhancement of anti-body dependent cell cytotoxicity. This mechanism provides long lasting effects of nucleic acids, thus reducing dosing regimens, improving compliance and maintenance therapy, reducing emergency situations and improving quality of life.

Dwg.0/0

L6 ANSWER 2 OF 4 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN

AN 2003-12819 BIOTECHDS

TI Treatment of a subject having, or at risk of developing cancer, involves the use of an immunostimulatory nucleic acid having a modified backbone in combination with a cancer medicament;
phosphorothioate-modified backbone poly-G nucleic acid transfer and expression in host cell for immunostimulant and gene therapy

AU **BRATZLER R L**; PETERSEN D M

PA BRATZLER R L; PETERSEN D M

PI US 2002156033 24 Oct 2002

AI US 2001-800266 5 Mar 2001

PRAI US 2001-800266 5 Mar 2001; US 2000-187214 3 Mar 2000

DT Patent

LA English
OS WPI: 2003-275279 [27]
AB DERWENT ABSTRACT:
NOVELTY - Treatment (T1) of a subject having cancer involves administering an immunostimulatory nucleic acid (1) having modified backbone and a cancer medicament (M1) selected from chemotherapeutic agent, immunotherapeutic agent, cancer vaccine or hormone therapy. The poly-G nucleic acid is not conjugated to (M1) and is free of **CpG** and T-rich motif.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) Treatment (T3) of a subject having or at risk of developing cancer involving administering an immunostimulatory nucleic acid selected from **CpG** nucleic acid or a non-**CpG** nucleic acid (where the nucleic acid has a phosphorothioate modified backbone) and a cancer medicament such as hormone therapy (HT); and (2) A device for delivering immunostimulatory nucleic acid to a subject receiving an intravenous injection, comprising an intravenous device (D1) selected from a bag or a tube and the nucleic acid, where the nucleic acid is coated on an internal surface of (D1) or is embedded within (D1).

ACTIVITY - Cytostatic; Fungicide; Antibacterial; Antiparasitic; Virucide; Antiallergic; Antianemic; Hemostatic.

MECHANISM OF ACTION - Cell growth inhibitor.

USE - The composition is for the treatment of cancer (e.g. bone cancer, brain and CNS cancer, connective tissue cancer, esophageal cancer, eye cancer, Hodgkin's lymphoma, larynx cancer, oral cavity cancer, skin cancer, and testicular cancer), and for preventing **allergic** responses in those receiving blood transfusions (all claimed). It is also useful for the treatment of fungal, bacterial, parasitic and viral infections.

ADMINISTRATION - Administration is oral, parenteral (including intramuscular or intravenous), intranasal, intratracheal, through inhalation, ocular, vaginal, buccal or rectal. No dosage given.

ADVANTAGE - The combination of the immunostimulatory nucleic acids and the cancer medicament is synergistic. The combination allows for the administration of higher doses of cancer medicaments without as many side effects, and allows for the administration of lower, sub-therapeutic doses of either compound, but with higher efficacy than would otherwise be achieved using such low doses. The immunostimulatory nucleic acids function by enhancement of anti-body dependent cell cytotoxicity. This mechanism provides long lasting effects of nucleic acids, thus reducing dosing regimens, improving compliance and maintenance therapy, reducing emergency situations and improving quality of life. (32 pages)

L6 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:570637 CAPLUS
DN 139:132442
TI Methods and products for enhancing immune responses using imidazoquinoline compounds in combination with modified immunostimulatory oligonucleotide
IN Krieg, Arthur M.; Schetter, Christian; **Bratzler, Robert L.**; Vollmer, Jorg; Jurk, Marion; Bauer, Stefan
PA University of Iowa Research Foundation, USA
SO U.S. Pat. Appl. Publ., 112 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003139364	A1	20030724	US 2002-272502	20021015
PRAI	US 2001-329208P	P	20011012		

AB The invention involves administration of an imidazoquinoline agent in combination with another therapeutic agent. The combination of drugs may be administered in synergistic amts. or in various dosages or at various

time schedules. The invention also relates to kits and compns. concerning the combination of drugs. The combinations can be used to enhance ADCC, stimulate immune responses and/or patient and treat certain disorders. Specifically, the imidazoquinoline compns. R-848 is used which is shown to be more potent inducer of proinflammatory cytokines NF-.kappa.B in 293T cells by reconstitution of TLR9 signaling through co-transfecting TLR9, TLR8 and TLR7 into 293T cell. Furthermore, **CpG** oligonucleotides (ODNs, in particular, **CpG** ODN #7909) and R-848 are tested either together or individually for their ability to augment a cytolytic T lymphocyte response against antigen (e.g., HBsAg) in vivo using mouse model. The combination of R-848 and **CpG** ODN together is shown to result in an additive effect; while no augmentation of the CTL response over antigen alone is obsd. using control ODN either alone or with R-848. The distribution of antibody isotype also shows **CpG** ODN produces higher levels of IgG2a antibodies regardless of whether R-848 is present, and R-848 appears to increase the level of IgG2a and decrease the level of IgG1 as compared to the antigen alone response.

L6 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:814840 CAPLUS
DN 137:342112
TI Immunostimulatory nucleic acids and cancer medicament combination therapy for the treatment of cancer
IN **Bratzler, Robert L.; Petersen, Deanna M.**
PA USA
SO U.S. Pat. Appl. Publ., 32 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002156033	A1	20021024	US 2001-800266	20010305
PRAI	US 2000-187214P	P	20000303		

AB The invention involves administration of an immunostimulatory nucleic acid in combination with a cancer medicament for the treatment or prevention of cancer in subjects. The combination of drugs are administered in synergistic amts. or in various dosages or at various time schedules. The invention also relates to kits and compns. concerning the combination of drugs.

=> d his

(FILE 'HOME' ENTERED AT 07:59:41 ON 17 SEP 2003)

FILE 'BIOSIS, MEDLINE, AGRICOLA, EMBASE, CABA, WPIDS, JAPIO, BIOTECHDS, LIFESCI, CAPLUS' ENTERED AT 08:01:24 ON 17 SEP 2003

```
                E BRATZLER ROBERT L/AU
L1             41 S E1-E3
                E PETERSEN DEANNA M/AU
L2              7 S E3
                E FOURON YVES/AU
L3             31 S E1-E3
L4             73 S L1-L3
L5              5 S L4 AND (ASTHMA OR ALLERGIC OR ALLERGY)
L6              4 S L5 AND CPG
```

=> s l4 and (cpg or immunostimulatory or nucleic acid)
L7 27 L4 AND (CPG OR IMMUNOSTIMULATORY OR NUCLEIC ACID)

=> dup rem l7
PROCESSING COMPLETED FOR L7

L8 11 DUP REM L7 (16 DUPLICATES REMOVED)

=> d bib ab 1-11

L8 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:570637 CAPLUS
DN 139:132442
TI Methods and products for enhancing immune responses using imidazoquinoline compounds in combination with modified **immunostimulatory** oligonucleotide
IN Krieg, Arthur M.; Schetter, Christian; **Bratzler, Robert L.**; Vollmer, Jorg; Jurk, Marion; Bauer, Stefan
PA University of Iowa Research Foundation, USA
SO U.S. Pat. Appl. Publ., 112 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2003139364	A1	20030724	US 2002-272502	20021015
PRAI US 2001-329208P	P	20011012		

AB The invention involves administration of an imidazoquinoline agent in combination with another therapeutic agent. The combination of drugs may be administered in synergistic amts. or in various dosages or at various time schedules. The invention also relates to kits and compns. concerning the combination of drugs. The combinations can be used to enhance ADCC, stimulate immune responses and/or patient and treat certain disorders. Specifically, the imidazoquinoline compns. R-848 is used which is shown to be more potent inducer of proinflammatory cytokines NF-.kappa.B in 293T cells by reconstitution of TLR9 signaling through co-transfecting TLR9, TLR8 and TLR7 into 293T cell. Furthermore, **CpG** oligonucleotides (ODNs, in particular, **CpG** ODN #7909) and R-848 are tested either together or individually for their ability to augment a cytolytic T lymphocyte response against antigen (e.g., HBsAg) in vivo using mouse model. The combination of R-848 and **CpG** ODN together is shown to result in an additive effect; while no augmentation of the CTL response over antigen alone is obsd. using control ODN either alone or with R-848. The distribution of antibody isotype also shows **CpG** ODN produces higher levels of IgG2a antibodies regardless of whether R-848 is present, and R-848 appears to increase the level of IgG2a and decrease the level of IgG1 as compared to the antigen alone response.

L8 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:355834 CAPLUS
DN 138:362665
TI **Immunostimulatory** nucleic acids for the treatment of asthma and allergy
IN **Bratzler, Robert L.**; **Petersen, Deanna M.**; **Fouron, Yves**
PA USA
SO U.S. Pat. Appl. Publ., 221 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2003087848	A1	20030508	US 2001-776479	20010202
PRAI US 2000-179991P	P	20000203		

OS MARPAT 138:362665
AB The invention involves administration of an **immunostimulatory nucleic acid** alone or in combination with an

asthma/allergy medicament for the treatment or prevention of asthma and allergy in subjects. The combination of drugs are administered in synergistic amts. or in various dosages or at various time schedules. The invention also relates to kits and compns. concerning the combination of drugs.

L8 ANSWER 3 OF 11 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN DUPLICATE 1
AN 2002-566690 [60] WPIDS
DNC C2002-160648
TI Inhibiting angiogenesis in a subject, involves administering at least one antiangiogenic **nucleic acid** molecule to the subject.
DC B04 D16
IN **BRATZLER, R L**
PA (BRAT-I) BRATZLER R L; (COLE-N) COLEY PHARM GROUP INC
CYC 100
PI WO 2002053141 A2 20020711 (200260)* EN 276p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZW
US 2003055014 A1 20030320 (200323)
ADT WO 2002053141 A2 WO 2001-US48458 20011214; US 2003055014 A1 Provisional US 2000-255534P 20001214, US 2001-17995 20011214
PRAI US 2000-255534P 20001214; US 2001-17995 20011214
AB WO 200253141 A UPAB: 20020919
NOVELTY - Inhibiting (M1) angiogenesis in a subject, comprising administering at least one antiangiogenic **nucleic acid** molecule (I), is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit (K) comprising a first container housing (I), and instructions for administering (I) to a subject having a condition characterized by unwanted angiogenesis.

ACTIVITY - Cytostatic; Antirheumatic; Antiarthritic; Antipsoriatic; Antidiabetic; Ophthalmological; Immunosuppressive; Cardiant; Vasotropic; Vulnerary; Hemostatic; Dermatological; Antiarteriosclerotic.

MECHANISM OF ACTION - Inhibitor of angiogenesis; Gene therapy.

For each group of 5 mice, Matrigel (RTM) (M) was prepared as follows: For Group 1, (M) alone. For Group 2, (M)+basic fibroblast growth factor (FGF) (150 ng/ml)+heparin (40 units/ml). For Group 3, (M)+bFGF (150 ng/ml)+heparin (40 units/ml)+oligo 1826 (1 mg/ml). For Group 4, (M)+bFGF (150ng/ml)+heparin (40 units/ml) (this group received daily SC injections, for 6 days, of 100 micro l of oligonucleotide 1826 (1 mg/ml) on the opposite flank from (M) plug). All the groups received 500 micro l/mouse of the Matrigel or Matrigel compositions through subcutaneous route to the right of center of the abdomen. On day 6, the animals were euthanized and (M) plugs collected. The plugs were placed in 0.3 ml of sterile phosphateb buffered saline (PBS) and placed at 4 deg. C over night to allow liquefaction of (M). The hemoglobin and total protein content of (M) plugs was determined. When angiogenic factors were added to (M) (Group 2), there was a significant increase in the amount of hemoglobin present in (M) plug at 6 days when compared to (M) alone (Group 1) (p is less than 0.05). When **CpG** was included in (M) plug along with the angiogenic factors (Group 3), there was a greater than 2 fold decrease in the amount of hemoglobin present in (M) plug at 6 days when compared to (M) containing the angiogenic factors (Group 2). When **CpG** was administered daily by subcutaneous injection, rather than present in (M) plug, to the mouse in the flank opposite to (M) plug which contained angiogenic factors (Group 4) there was no significant difference in the amount of hemoglobin present in (M) plug at 6 days when compared to (M) containing the angiogenic factors (Group 2). The preliminary results suggested that the inclusion of **CpG** oligonucleotide directly within (M) (Group 3)

had a negative influence on angiogenesis. Although daily delivery of **CpG** to the opposite flank from (M) plug did not appear to influence angiogenesis, it is possible that **CpG** administered intravenously or subcutaneously in a region closer to the plug (and accordingly tumor mass) would manifest anti-angiogenic activity.

USE - M1 is useful for inhibiting angiogenesis associated with solid tumor growth, tumor metastasis, precancerous lesion, rheumatoid arthritis, psoriasis, diabetic retinopathy, retinopathy or prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, Osler-Webber Syndrome, myocardial angiogenesis, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma, wound granulation, intestinal adhesions, atherosclerosis, scleroderma and hypertrophic scars (claimed).

Dwg.0/1

L8 ANSWER 4 OF 11 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN DUPLICATE 2
AN 2003-370798 [35] WPIDS
DNC C2003-098210
TI Prevention or treatment of gastric ulcer involves administering **nucleic acid**.
DC B04 D16
IN **BRATZLER, R L**; PETERSEN, D M
PA (BRAT-I) BRATZLER R L; (PETE-I) PETERSEN D M
CYC 1
PI US 2002198165 A1 20021226 (200335)* 45p
ADT US 2002198165 A1 Provisional US 2000-222248P 20000801, US 2001-920313 20010801
PRAI US 2000-222248P 20000801; US 2001-920313 20010801
AB US2002198165 A UPAB: 20030603
NOVELTY - Prevention (M) or treatment of gastric ulcer comprising administering a **nucleic acid** to a subject in need for treatment of gastric ulcer, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit comprising at least one container housing **nucleic acid**, an anti-ulcer agent, and instructions for administering the **nucleic acid** and the anti-ulcer agent to a subject having an ulcer or at risk of developing an ulcer.

ACTIVITY - Antiulcer.

A **nucleic acid** sample comprising oligonucleotide 2006 was administered to a mouse model by an oral route or a vehicle control. Colonization of mice by H. pylori was assessed at time points from 1 day to 1 month after treatment. The ability of the **nucleic acid** to reduce H.pylori colonization was assessed.

USE - M is useful for preventing or treating a gastric ulcer on a subject, e.g. human or non-human vertebrate animal including dog, cat, horse, cow, goat, sheep, pig, rabbit, turkey, chicken, primate, rat, and mouse.

ADVANTAGE - M effectively treats or prevents gastric ulcers.

Dwg.0/0

L8 ANSWER 5 OF 11 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN DUPLICATE 3
AN 2003-166150 [16] WPIDS
DNC C2003-043117
TI Pharmaceutical composition for treatment of anemia, thrombocytopenia and neutropenia comprises an **immunostimulatory nucleic acid** and a medicament for the respective disease.
DC B05
IN **BRATZLER, R L**; PETERSEN, D M; SCHETTER, C
PA (BRAT-I) BRATZLER R L; (PETE-I) PETERSEN D M; (SCHE-I) SCHETTER C
CYC 1
PI US 2002165178 A1 20021107 (200316)* 27p
ADT US 2002165178 A1 Provisional US 2000-214368P 20000628, US 2001-895007 20010628

PRAI US 2000-214368P 20000628; US 2001-895007 20010628
AB US2002165178 A UPAB: 20030307
NOVELTY - A pharmaceutical composition comprises an **immunostimulatory nucleic acid** (A) and either an anemia medicament (B), thrombocytopenia medicament (B1) or a neutropenia medicament (B2) formulated in a carrier.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) decreasing the dose of (B), (B1) or (B2) involving administering (B), (B1) or (B2) in a subtherapeutic dosage and (A);

(2) treating or preventing anemia, thrombocytopenia or neutropenia involving administering (A) selected from a methylated **CpG nucleic acid**, a T-rich **nucleic acid**, a poly-G **nucleic acid** and/or a **nucleic acid** having a phosphorothioate backbone. (A) Having a phosphorothioate backbone is not a **CpG nucleic acid**; and

(3) increasing the dose of (B2) involving administering (B2) in a dose which ordinarily induces side effects, and administering (A) to prevent the induction of side effects by (B2).

ACTIVITY - Antianemic; Thrombolytic; Hemostatic; Immunostimulant.

MECHANISM OF ACTION - None given.

USE - For the treatment or prevention of anemia, thrombocytopenia and neutropenia in a subject preparing to undergo chemotherapy, radiation treatment, and has received at least one dose of chemotherapy or radiation treatment (claimed).

ADVANTAGE - The composition provides a synergistic effect; permits a lower dose of the medicament to be used, thus providing lower costs associated using lower doses of the medicament and reduced chances of inducing side effects. The efficacy of the combination is profoundly improved over the use of each of the medicaments alone.

Dwg.0/1

L8 ANSWER 6 OF 11 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN DUPLICATE 4
AN 2003-275279 [27] WPIDS
DNC C2003-072415
TI Treatment of a subject having, or at risk of developing cancer, involves the use of an **immunostimulatory nucleic acid** having a modified backbone in combination with a cancer medicament.
DC B05
IN **BRATZLER, R L**; PETERSEN, D M
PA (BRAT-I) BRATZLER R L; (PETE-I) PETERSEN D M
CYC 1
PI US 2002156033 A1 20021024 (200327)* 32p
ADT US 2002156033 A1 Provisional US 2000-187214P 20000303, US 2001-800266 20010305
PRAI US 2000-187214P 20000303; US 2001-800266 20010305
AB US2002156033 A UPAB: 20030429
NOVELTY - Treatment (T1) of a subject having cancer involves administering an **immunostimulatory nucleic acid** (1) having modified backbone and a cancer medicament (M1) selected from chemotherapeutic agent, immunotherapeutic agent, cancer vaccine or hormone therapy. The poly-G **nucleic acid** is not conjugated to (M1) and is free of **CpG** and T-rich motif.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) Treatment (T3) of a subject having or at risk of developing cancer involving administering an **immunostimulatory nucleic acid** selected from **CpG nucleic acid** or a non-**CpG nucleic acid** (where the **nucleic acid** has a phosphorothioate modified backbone) and a cancer medicament such as hormone therapy (HT); and

(2) A device for delivering **immunostimulatory**

nucleic acid to a subject receiving an intravenous injection, comprising an intravenous device (D1) selected from a bag or a tube and the **nucleic acid**, where the **nucleic acid** is coated on an internal surface of (D1) or is embedded within (D1).

ACTIVITY - Cytostatic; Fungicide; Antibacterial; Antiparasitic; Virucide; Antiallergic; Antianemic; Hemostatic.

MECHANISM OF ACTION - Cell growth inhibitor.

USE - The composition is for the treatment of cancer (e.g. bone cancer, brain and CNS cancer, connective tissue cancer, esophageal cancer, eye cancer, Hodgkin's lymphoma, larynx cancer, oral cavity cancer, skin cancer, and testicular cancer), and for preventing allergic responses in those receiving blood transfusions (all claimed). It is also useful for the treatment of fungal, bacterial, parasitic and viral infections.

ADVANTAGE - The combination of the **immunostimulatory** nucleic acids and the cancer medicament is synergistic. The combination allows for the administration of higher doses of cancer medicaments without as many side effects, and allows for the administration of lower, sub-therapeutic doses of either compound, but with higher efficacy than would otherwise be achieved using such low doses. The **immunostimulatory** nucleic acids function by enhancement of anti-body dependent cell cytotoxicity. This mechanism provides long lasting effects of nucleic acids, thus reducing dosing regimens, improving compliance and maintenance therapy, reducing emergency situations and improving quality of life.

Dwg.0/0

L8 ANSWER 7 OF 11 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN DUPLICATE 5
AN 2002-665650 [71] WPIDS
DNC C2002-186885
TI Preventing/treating sexually transmitted disease by administering a poly-G **nucleic acid**, a non-motif phosphorothioate **nucleic acid** or a **nucleic acid** to induce an immune response at a local site in the subject.
DC B04 D16
IN **BRATZLER, R L**; PETERSEN, D M
PA (BRAT-I) BRATZLER R L; (PETE-I) PETERSEN D M
CYC 1
PI US 2002091097 A1 20020711 (200271)* 24p
ADT US 2002091097 A1 Provisional US 2000-230637P 20000907, US 2001-949194 20010907
PRAI US 2000-230637P 20000907; US 2001-949194 20010907
AB US2002091097 A UPAB: 20021105

NOVELTY - Preventing or treating (M) a sexually transmitted disease (STD) involves administering to a subject, a poly-G **nucleic acid**, a non-motif phosphorothioate **nucleic acid** or a **nucleic acid** to induce an immune response at a local site in the subject.

DETAILED DESCRIPTION - (M) involves administering to a subject a poly-G **nucleic acid**, a non-motif phosphorothioate **nucleic acid** or a **nucleic acid** to induce an immune response at a local site in the subject, where the subject is at risk of exposure to the local site to an agent that causes STD, such as Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum, Haemophilus ducreyi, Condyloma acuminata, Calymmatobacterium granulomatis, Ureaplasma urealyticum, human T lymphotropic virus type I (HTLV-I), human papilloma virus (multiple types), molluscum contagiosum virus, Trichomonas vaginalis, Phthirus pubis, Candida albicans, Mycoplasma hominis, Gardnerella vaginalis, group B Streptococcus, HTLV-II, hepatitis A, B, C and D viruses, Epstein-Barr virus (EBV), Sarcoptes scabiei, Shigella spp., Campylobacter spp., Giardia lamblia, and Entamoeba histolytica; especially a poly-G **nucleic acid**, where subject is not actively exposed to an antigen and is at risk of exposure

at the local site to an agent such as herpes simplex virus type 1 and 2 (HSV1 and HSV2), human papilloma virus (multiple types), HCV, HDV, EBV; especially a non-motif phosphorothioate **nucleic acid**, where subject is at a risk of exposure to human immunodeficiency viruses (HIV-1 and HIV-2), EBV, and cytomegalovirus.

INDEPENDENT CLAIMS are also included for the following:

(1) a non-vaccine composition (I) comprising a **CpG nucleic acid** formulated in a sustained release device in an effective amount, where the **nucleic acid** does not encode a peptide or polypeptide;

(2) a composition (II) comprising a **nucleic acid** such as poly-G **nucleic acid** and a non-motif phosphorothioate **nucleic acid**, formulated in a sustained release device in an effective amount;

(3) a composition (III) comprising a **nucleic acid** ; and a birth control agent, or a birth control device, or an intravenous bag, where the **nucleic acid** is situated within the intravenous bag, or a diaper, where the **nucleic acid** is contained within or on the surface of the diaper; and

(4) a kit (IV) comprising the above compositions, and instructions for administering the composition to a subject having or at risk of developing STD.

ACTIVITY - Antibacterial; Virucide; Anti-HIV; Hepatotropic; Antiinflammatory; Protozoacide; Fungicide; Cytostatic; Antiallergic; Dermatological; Antiarthritic; Antiulcer.

MECHANISM OF ACTION - Inducer of immune response. Test details are described but no results are given.

USE - (M), (I), (II) and (III) are useful for treating or preventing STD caused by the above mentioned viruses, bacteria, protozoa and fungi (claimed), such as AIDS, chancroid, chlamydia, gonorrhoeae, hepatitis, syphilis, trichomonas, venereal warts, pelvic inflammatory disease, pubic lice, scabies, candidiasis, monilial vaginitis and STD-related conditions neoplasias, allergies, acute arthritis, bacterial vaginosis, urethritis, enteritis, enterocolitis, epidymitis, epididymo-or-chitis, Kaposi's sarcoma, gonococcal dermititis, lymphoid neoplasia, mononucleosis syndrome, pharyngitis, proctocolitis, prostatitis, septicemia, tropical spastic paraparesis, ulcerative lesions of the genitalia or squamous cell cancer of the cervis, anus, vulva or penis.

Dwg.0/0

L8 ANSWER 8 OF 11 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN DUPLICATE 6
AN 2001-290487 [30] WPIDS
DNC C2001-088963
TI Improving the efficacy of treatments involving the administration of interferon-alpha by co-administering an isolated **immunostimulatory nucleic acid**.
DC B04 D16
IN **BRATZLER, R L**; HARTMANN, G; KRIEG, A; KRIEG, A M
PA (COLE-N) COLEY PHARM GROUP INC; (IOWA) UNIV IOWA RES FOUND; (COLE-N) COLEY PHARM GMBH
CYC 94
PI WO 2001022990 A2 20010405 (200130)* EN 166p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000076190 A 20010430 (200142)
EP 1220684 A2 20020710 (200253) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2003510290 W 20030318 (200321) 197p

9/776479

```
=> e bratzler robert l/au
E1            2     BRATZLER R/AU
E2           25     BRATZLER R L/AU
E3           14 --> BRATZLER ROBERT L/AU
E4           15     BRATZLER U/AU
E5            1     BRATZLER UWE/AU
E6            1     BRATZSLAVSKAYA O I/AU
E7            4     BRAU/AU
E8           55     BRAU A/AU
E9            3     BRAU A C S/AU
E10           1     BRAU AGADE E/AU
E11           1     BRAU AGAUDE E/AU
E12          17     BRAU AGUADE E/AU

=> s e1-e3
L1           41 ("BRATZLER R"/AU OR "BRATZLER R L"/AU OR "BRATZLER ROBERT L"/AU)


=> e petersen deanna m/au
E1            3     PETERSEN DAVID A/AU
E2            4     PETERSEN DAVID M/AU
E3            7 --> PETERSEN DEANNA M/AU
E4            1     PETERSEN DEBBIE/AU
E5            1     PETERSEN DEBORAH J/AU
E6            2     PETERSEN DEBORAH W/AU
E7            3     PETERSEN DEBORAH WISSINK/AU
E8           20     PETERSEN DEN BESTEN A/AU
E9            2     PETERSEN DEN BESTEN ANNELIEN/AU
E10          12     PETERSEN DENISE/AU
E11           1     PETERSEN DENISE M/AU
E12           2     PETERSEN DENNIS E/AU

=> s e3
L2            7 "PETERSEN DEANNA M"/AU

=> e fouron yves/au
E1           17     FOURON Y/AU
E2            1     FOURON Y M F/AU
E3           13 --> FOURON YVES/AU
E4            1     FOURONIE A/AU
E5            9     FOUROT BAUZON M/AU
E6            2     FOUROT H/AU
E7            6     FOUROT J/AU
E8            5     FOUROT M/AU
E9            1     FOUROT Y/AU
E10           3     FOUROUCLAS N/AU
E11           1     FOUROUET J L/AU
E12           1     FOUROUET J P/AU

=> s e1-e3
L3           31 ("FOURON Y"/AU OR "FOURON Y M F"/AU OR "FOURON YVES"/AU)

=> s l1-l3
L4           73 (L1 OR L2 OR L3)

=> s l4 and (asthma or allergic or allergy)
L5            5 L4 AND (ASTHMA OR ALLERGIC OR ALLERGY)

=> s l5 and cpg
L6            4 L5 AND CPG

=> d bib ab 1-4

L6   ANSWER 1 OF 4  WPIDS  COPYRIGHT 2003 THOMSON DERWENT on STN
```

AN 2003-275279 [27] WPIDS
DNC C2003-072415
TI Treatment of a subject having, or at risk of developing cancer, involves the use of an immunostimulatory nucleic acid having a modified backbone in combination with a cancer medicament.
DC B05
IN **BRATZLER, R L**; PETERSEN, D M
PA (BRAT-I) BRATZLER R L; (PETE-I) PETERSEN D M
CYC 1
PI US 2002156033 A1 20021024 (200327)* 32p
ADT US 2002156033 A1 Provisional US 2000-187214P 20000303, US 2001-800266 20010305
PRAI US 2000-187214P 20000303; US 2001-800266 20010305
AB US2002156033 A UPAB: 20030429
NOVELTY - Treatment (T1) of a subject having cancer involves administering an immunostimulatory nucleic acid (1) having modified backbone and a cancer medicament (M1) selected from chemotherapeutic agent, immunotherapeutic agent, cancer vaccine or hormone therapy. The poly-G nucleic acid is not conjugated to (M1) and is free of **CpG** and T-rich motif.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) Treatment (T3) of a subject having or at risk of developing cancer involving administering an immunostimulatory nucleic acid selected from **CpG** nucleic acid or a non-**CpG** nucleic acid (where the nucleic acid has a phosphorothioate modified backbone) and a cancer medicament such as hormone therapy (HT); and

(2) A device for delivering immunostimulatory nucleic acid to a subject receiving an intravenous injection, comprising an intravenous device (D1) selected from a bag or a tube and the nucleic acid, where the nucleic acid is coated on an internal surface of (D1) or is embedded within (D1).

ACTIVITY - Cytostatic; Fungicide; Antibacterial; Antiparasitic; Virucide; Antiallergic; Antianemic; Hemostatic.

MECHANISM OF ACTION - Cell growth inhibitor.

USE - The composition is for the treatment of cancer (e.g. bone cancer, brain and CNS cancer, connective tissue cancer, esophageal cancer, eye cancer, Hodgkin's lymphoma, larynx cancer, oral cavity cancer, skin cancer, and testicular cancer), and for preventing **allergic** responses in those receiving blood transfusions (all claimed). It is also useful for the treatment of fungal, bacterial, parasitic and viral infections.

ADVANTAGE - The combination of the immunostimulatory nucleic acids and the cancer medicament is synergistic. The combination allows for the administration of higher doses of cancer medicaments without as many side effects, and allows for the administration of lower, sub-therapeutic doses of either compound, but with higher efficacy than would otherwise be achieved using such low doses. The immunostimulatory nucleic acids function by enhancement of anti-body dependent cell cytotoxicity. This mechanism provides long lasting effects of nucleic acids, thus reducing dosing regimens, improving compliance and maintenance therapy, reducing emergency situations and improving quality of life.

Dwg.0/0

L6 ANSWER 2 OF 4 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AN 2003-12819 BIOTECHDS
TI Treatment of a subject having, or at risk of developing cancer, involves the use of an immunostimulatory nucleic acid having a modified backbone in combination with a cancer medicament;
phosphorothioate-modified backbone poly-G nucleic acid transfer and expression in host cell for immunostimulant and gene therapy
AU **BRATZLER R L**; PETERSEN D M
PA BRATZLER R L; PETERSEN D M
PI US 2002156033 24 Oct 2002
AI US 2001-800266 5 Mar 2001

PRAI US 2001-800266 5 Mar 2001; US 2000-187214 3 Mar 2000
DT Patent
LA English
OS WPI: 2003-275279 [27]
AB DERWENT ABSTRACT:
NOVELTY - Treatment (T1) of a subject having cancer involves administering an immunostimulatory nucleic acid (1) having modified backbone and a cancer medicament (M1) selected from chemotherapeutic agent, immunotherapeutic agent, cancer vaccine or hormone therapy. The poly-G nucleic acid is not conjugated to (M1) and is free of **CpG** and T-rich motif.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) Treatment (T3) of a subject having or at risk of developing cancer involving administering an immunostimulatory nucleic acid selected from **CpG** nucleic acid or a non-**CpG** nucleic acid (where the nucleic acid has a phosphorothioate modified backbone) and a cancer medicament such as hormone therapy (HT); and (2) A device for delivering immunostimulatory nucleic acid to a subject receiving an intravenous injection, comprising an intravenous device (D1) selected from a bag or a tube and the nucleic acid, where the nucleic acid is coated on an internal surface of (D1) or is embedded within (D1).

ACTIVITY - Cytostatic; Fungicide; Antibacterial; Antiparasitic; Virucide; Antiallergic; Antianemic; Hemostatic.

MECHANISM OF ACTION - Cell growth inhibitor.

USE - The composition is for the treatment of cancer (e.g. bone cancer, brain and CNS cancer, connective tissue cancer, esophageal cancer, eye cancer, Hodgkin's lymphoma, larynx cancer, oral cavity cancer, skin cancer, and testicular cancer), and for preventing **allergic** responses in those receiving blood transfusions (all claimed). It is also useful for the treatment of fungal, bacterial, parasitic and viral infections.

ADMINISTRATION - Administration is oral, parenteral (including intramuscular or intravenous), intranasal, intratracheal, through inhalation, ocular, vaginal, buccal or rectal. No dosage given.

ADVANTAGE - The combination of the immunostimulatory nucleic acids and the cancer medicament is synergistic. The combination allows for the administration of higher doses of cancer medicaments without as many side effects, and allows for the administration of lower, sub-therapeutic doses of either compound, but with higher efficacy than would otherwise be achieved using such low doses. The immunostimulatory nucleic acids function by enhancement of anti-body dependent cell cytotoxicity. This mechanism provides long lasting effects of nucleic acids, thus reducing dosing regimens, improving compliance and maintenance therapy, reducing emergency situations and improving quality of life. (32 pages)

L6 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:570637 CAPLUS
DN 139:132442
TI Methods and products for enhancing immune responses using imidazoquinoline compounds in combination with modified immunostimulatory oligonucleotide
IN Krieg, Arthur M.; Schetter, Christian; **Bratzler, Robert L.**; Vollmer, Jorg; Jurk, Marion; Bauer, Stefan
PA University of Iowa Research Foundation, USA
SO U.S. Pat. Appl. Publ., 112 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2003139364	A1	20030724	US 2002-272502	20021015
PRAI US 2001-329208P	P	20011012		

AB The invention involves administration of an imidazoquinoline agent in combination with another therapeutic agent. The combination of drugs may

be administered in synergistic amts. or in various dosages or at various time schedules. The invention also relates to kits and compns. concerning the combination of drugs. The combinations can be used to enhance ADCC, stimulate immune responses and/or patient and treat certain disorders. Specifically, the imidazoquinoline compns. R-848 is used which is shown to be more potent inducer of proinflammatory cytokines NF-.kappa.B in 293T cells by reconstitution of TLR9 signaling through co-transfecting TLR9, TLR8 and TLR7 into 293T cell. Furthermore, **CpG** oligonucleotides (ODNs, in particular, **CpG** ODN #7909) and R-848 are tested either together or individually for their ability to augment a cytolytic T lymphocyte response against antigen (e.g., HBsAg) in vivo using mouse model. The combination of R-848 and **CpG** ODN together is shown to result in an additive effect; while no augmentation of the CTL response over antigen alone is obsd. using control ODN either alone or with R-848. The distribution of antibody isotype also shows **CpG** ODN produces higher levels of IgG2a antibodies regardless of whether R-848 is present, and R-848 appears to increase the level of IgG2a and decrease the level of IgG1 as compared to the antigen alone response.

L6 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:814840 CAPLUS
DN 137:342112
TI Immunostimulatory nucleic acids and cancer medicament combination therapy for the treatment of cancer
IN **Bratzler, Robert L.; Petersen, Deanna M.**
PA USA
SO U.S. Pat. Appl. Publ., 32 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002156033	A1	20021024	US 2001-800266	20010305
PRAI	US 2000-187214P	P	20000303		

AB The invention involves administration of an immunostimulatory nucleic acid in combination with a cancer medicament for the treatment or prevention of cancer in subjects. The combination of drugs are administered in synergistic amts. or in various dosages or at various time schedules. The invention also relates to kits and compns. concerning the combination of drugs.

=> d his

(FILE 'HOME' ENTERED AT 07:59:41 ON 17 SEP 2003)

FILE 'BIOSIS, MEDLINE, AGRICOLA, EMBASE, CABA, WPIDS, JAPIO, BIOTECHDS, LIFESCI, CAPLUS' ENTERED AT 08:01:24 ON 17 SEP 2003

```
                E BRATZLER ROBERT L/AU
L1             41 S E1-E3
                E PETERSEN DEANNA M/AU
L2              7 S E3
                E FOURON YVES/AU
L3             31 S E1-E3
L4             73 S L1-L3
L5              5 S L4 AND (ASTHMA OR ALLERGIC OR ALLERGY)
L6              4 S L5 AND CPG

=> s l4 and (cpg or immunostimulatory or nucleic acid)
L7             27 L4 AND (CPG OR IMMUNOSTIMULATORY OR NUCLEIC ACID)

=> dup rem l7
PROCESSING COMPLETED FOR L7
```

L8 11 DUP REM L7 (16 DUPLICATES REMOVED)

=> d bib ab 1-11

L8 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:570637 CAPLUS
DN 139:132442
TI Methods and products for enhancing immune responses using imidazoquinoline compounds in combination with modified **immunostimulatory** oligonucleotide
IN Krieg, Arthur M.; Schetter, Christian; **Bratzler, Robert L.**; Vollmer, Jorg; Jurk, Marion; Bauer, Stefan
PA University of Iowa Research Foundation, USA
SO U.S. Pat. Appl. Publ., 112 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2003139364	A1	20030724	US 2002-272502	20021015
PRAI US 2001-329208P	P	20011012		

AB The invention involves administration of an imidazoquinoline agent in combination with another therapeutic agent. The combination of drugs may be administered in synergistic amts. or in various dosages or at various time schedules. The invention also relates to kits and compns. concerning the combination of drugs. The combinations can be used to enhance ADCC, stimulate immune responses and/or patient and treat certain disorders. Specifically, the imidazoquinoline compns. R-848 is used which is shown to be more potent inducer of proinflammatory cytokines NF-.kappa.B in 293T cells by reconstitution of TLR9 signaling through co-transfecting TLR9, TLR8 and TLR7 into 293T cell. Furthermore, **CpG** oligonucleotides (ODNs, in particular, **CpG** ODN #7909) and R-848 are tested either together or individually for their ability to augment a cytolytic T lymphocyte response against antigen (e.g., HBsAg) in vivo using mouse model. The combination of R-848 and **CpG** ODN together is shown to result in an additive effect; while no augmentation of the CTL response over antigen alone is obsd. using control ODN either alone or with R-848. The distribution of antibody isotype also shows **CpG** ODN produces higher levels of IgG2a antibodies regardless of whether R-848 is present, and R-848 appears to increase the level of IgG2a and decrease the level of IgG1 as compared to the antigen alone response.

L8 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:355834 CAPLUS
DN 138:362665
TI **Immunostimulatory** nucleic acids for the treatment of asthma and allergy
IN **Bratzler, Robert L.**; **Petersen, Deanna M.**; **Fouron, Yves**
PA USA
SO U.S. Pat. Appl. Publ., 221 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2003087848	A1	20030508	US 2001-776479	20010202
PRAI US 2000-179991P	P	20000203		

OS MARPAT 138:362665
AB The invention involves administration of an **immunostimulatory nucleic acid** alone or in combination with an asthma/allergy medicament for the treatment or prevention of asthma and

allergy in subjects. The combination of drugs are administered in synergistic amts. or in various dosages or at various time schedules. The invention also relates to kits and compns. concerning the combination of drugs.

L8 ANSWER 3 OF 11 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN DUPLICATE 1
AN 2002-566690 [60] WPIDS
DNC C2002-160648
TI Inhibiting angiogenesis in a subject, involves administering at least one antiangiogenic **nucleic acid** molecule to the subject.
DC B04 D16
IN **BRATZLER, R L**
PA (BRAT-I) BRATZLER R L; (COLE-N) COLEY PHARM GROUP INC
CYC 100
PI WO 2002053141 A2 20020711 (200260)* EN 276p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZW
US 2003055014 A1 20030320 (200323)
ADT WO 2002053141 A2 WO 2001-US48458 20011214; US 2003055014 A1 Provisional US 2000-255534P 20001214, US 2001-17995 20011214
PRAI US 2000-255534P 20001214; US 2001-17995 20011214
AB WO 200253141 A UPAB: 20020919
NOVELTY - Inhibiting (M1) angiogenesis in a subject, comprising administering at least one antiangiogenic **nucleic acid** molecule (I), is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit (K) comprising a first container housing (I), and instructions for administering (I) to a subject having a condition characterized by unwanted angiogenesis.

ACTIVITY - Cytostatic; Antirheumatic; Antiarthritic; Antipsoriatic; Antidiabetic; Ophthalmological; Immunosuppressive; Cardiant; Vasotropic; Vulnerary; Hemostatic; Dermatological; Antiarteriosclerotic.

MECHANISM OF ACTION - Inhibitor of angiogenesis; Gene therapy.

For each group of 5 mice, Matrigel (RTM) (M) was prepared as follows: For Group 1, (M) alone. For Group 2, (M)+basic fibroblast growth factor (FGF) (150 ng/ml)+heparin (40 units/ml). For Group 3, (M)+bFGF (150 ng/ml)+heparin (40 units/ml)+oligo 1826 (1 mg/ml). For Group 4, (M)+bFGF (150ng/ml)+heparin (40 units/ml) (this group received daily SC injections, for 6 days, of 100 micro l of oligonucleotide 1826 (1 mg/ml) on the opposite flank from (M) plug). All the groups received 500 micro l/mouse of the Matrigel or Matrigel compositions through subcutaneous route to the right of center of the abdomen. On day 6, the animals were euthanized and (M) plugs collected. The plugs were placed in 0.3 ml of sterile phosphateb buffered saline (PBS) and placed at 4 deg. C over night to allow liquefaction of (M). The hemoglobin and total protein content of (M) plugs was determined. When angiogenic factors were added to (M) (Group 2), there was a significant increase in the amount of hemoglobin present in (M) plug at 6 days when compared to (M) alone (Group 1) (p is less than 0.05). When **CpG** was included in (M) plug along with the angiogenic factors (Group 3), there was a greater than 2 fold decrease in the amount of hemoglobin present in (M) plug at 6 days when compared to (M) containing the angiogenic factors (Group 2). When **CpG** was administered daily by subcutaneous injection, rather than present in (M) plug, to the mouse in the flank opposite to (M) plug which contained angiogenic factors (Group 4) there was no significant difference in the amount of hemoglobin present in (M) plug at 6 days when compared to (M) containing the angiogenic factors (Group 2). The preliminary results suggested that the inclusion of **CpG** oligonucleotide directly within (M) (Group 3) had a negative influence on angiogenesis. Although daily delivery of **CpG** to the opposite flank from (M) plug did not appear to

influence angiogenesis, it is possible that **CpG** administered intravenously or subcutaneously in a region closer to the plug (and accordingly tumor mass) would manifest anti-angiogenic activity.

USE - M1 is useful for inhibiting angiogenesis associated with solid tumor growth, tumor metastasis, precancerous lesion, rheumatoid arthritis, psoriasis, diabetic retinopathy, retinopathy or prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, Osler-Webber Syndrome, myocardial angiogenesis, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma, wound granulation, intestinal adhesions, atherosclerosis, scleroderma and hypertrophic scars (claimed).

Dwg.0/1

L8 ANSWER 4 OF 11 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN DUPLICATE 2
AN 2003-370798 [35] WPIDS
DNC C2003-098210
TI Prevention or treatment of gastric ulcer involves administering **nucleic acid**.
DC B04 D16
IN **BRATZLER, R L**; PETERSEN, D M
PA (BRAT-I) BRATZLER R L; (PETE-I) PETERSEN D M
CYC 1
PI US 2002198165 A1 20021226 (200335)* 45p
ADT US 2002198165 A1 Provisional US 2000-222248P 20000801, US 2001-920313 20010801
PRAI US 2000-222248P 20000801; US 2001-920313 20010801
AB US2002198165 A UPAB: 20030603
NOVELTY - Prevention (M) or treatment of gastric ulcer comprising administering a **nucleic acid** to a subject in need for treatment of gastric ulcer, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit comprising at least one container housing **nucleic acid**, an anti-ulcer agent, and instructions for administering the **nucleic acid** and the anti-ulcer agent to a subject having an ulcer or at risk of developing an ulcer.

ACTIVITY - Antiulcer.

A **nucleic acid** sample comprising oligonucleotide 2006 was administered to a mouse model by an oral route or a vehicle control. Colonization of mice by H. pylori was assessed at time points from 1 day to 1 month after treatment. The ability of the **nucleic acid** to reduce H.pylori colonization was assessed.

USE - M is useful for preventing or treating a gastric ulcer on a subject, e.g. human or non-human vertebrate animal including dog, cat, horse, cow, goat, sheep, pig, rabbit, turkey, chicken, primate, rat, and mouse.

ADVANTAGE - M effectively treats or prevents gastric ulcers.

Dwg.0/0

L8 ANSWER 5 OF 11 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN DUPLICATE 3
AN 2003-166150 [16] WPIDS
DNC C2003-043117
TI Pharmaceutical composition for treatment of anemia, thrombocytopenia and neutropenia comprises an **immunostimulatory nucleic acid** and a medicament for the respective disease.
DC B05
IN **BRATZLER, R L**; PETERSEN, D M; SCHETTER, C
PA (BRAT-I) BRATZLER R L; (PETE-I) PETERSEN D M; (SCHE-I) SCHETTER C
CYC 1
PI US 2002165178 A1 20021107 (200316)* 27p
ADT US 2002165178 A1 Provisional US 2000-214368P 20000628, US 2001-895007 20010628
PRAI US 2000-214368P 20000628; US 2001-895007 20010628
AB US2002165178 A UPAB: 20030307
NOVELTY - A pharmaceutical composition comprises an

immunostimulatory nucleic acid (A) and either an anemia medicament (B), thrombocytopenia medicament (B1) or a neutropenia medicament (B2) formulated in a carrier.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) decreasing the dose of (B), (B1) or (B2) involving administering (B), (B1) or (B2) in a subtherapeutic dosage and (A);

(2) treating or preventing anemia, thrombocytopenia or neutropenia involving administering (A) selected from a methylated **CpG nucleic acid**, a T-rich **nucleic acid**, a poly-G **nucleic acid** and/or a **nucleic acid** having a phosphorothioate backbone. (A) Having a phosphorothioate backbone is not a **CpG nucleic acid**; and

(3) increasing the dose of (B2) involving administering (B2) in a dose which ordinarily induces side effects, and administering (A) to prevent the induction of side effects by (B2).

ACTIVITY - Antianemic; Thrombolytic; Hemostatic; Immunostimulant.

MECHANISM OF ACTION - None given.

USE - For the treatment or prevention of anemia, thrombocytopenia and neutropenia in a subject preparing to undergo chemotherapy, radiation treatment, and has received at least one dose of chemotherapy or radiation treatment (claimed).

ADVANTAGE - The composition provides a synergistic effect; permits a lower dose of the medicament to be used, thus providing lower costs associated using lower doses of the medicament and reduced chances of inducing side effects. The efficacy of the combination is profoundly improved over the use of each of the medicaments alone.

Dwg.0/1

L8 ANSWER 6 OF 11 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN DUPLICATE 4
AN 2003-275279 [27] WPIDS
DNC C2003-072415
TI Treatment of a subject having, or at risk of developing cancer, involves the use of an **immunostimulatory nucleic acid** having a modified backbone in combination with a cancer medicament.
DC B05
IN **BRATZLER, R L**; PETERSEN, D M
PA (BRAT-I) BRATZLER R L; (PETE-I) PETERSEN D M
CYC 1
PI US 2002156033 A1 20021024 (200327)* 32p
ADT US 2002156033 A1 Provisional US 2000-187214P 20000303, US 2001-800266 20010305
PRAI US 2000-187214P 20000303; US 2001-800266 20010305
AB US2002156033 A UPAB: 20030429

NOVELTY - Treatment (T1) of a subject having cancer involves administering an **immunostimulatory nucleic acid** (1) having modified backbone and a cancer medicament (M1) selected from chemotherapeutic agent, immunotherapeutic agent, cancer vaccine or hormone therapy. The poly-G **nucleic acid** is not conjugated to (M1) and is free of **CpG** and T-rich motif.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) Treatment (T3) of a subject having or at risk of developing cancer involving administering an **immunostimulatory nucleic acid** selected from **CpG nucleic acid** or a non-**CpG nucleic acid** (where the **nucleic acid** has a phosphorothioate modified backbone) and a cancer medicament such as hormone therapy (HT); and

(2) A device for delivering **immunostimulatory nucleic acid** to a subject receiving an intravenous injection, comprising an intravenous device (D1) selected from a bag or a tube and the **nucleic acid**, where the **nucleic acid** is coated on an internal surface of (D1) or is embedded

within (D1).

ACTIVITY - Cytostatic; Fungicide; Antibacterial; Antiparasitic; Virucide; Antiallergic; Antianemic; Hemostatic.

MECHANISM OF ACTION - Cell growth inhibitor.

USE - The composition is for the treatment of cancer (e.g. bone cancer, brain and CNS cancer, connective tissue cancer, esophageal cancer, eye cancer, Hodgkin's lymphoma, larynx cancer, oral cavity cancer, skin cancer, and testicular cancer), and for preventing allergic responses in those receiving blood transfusions (all claimed). It is also useful for the treatment of fungal, bacterial, parasitic and viral infections.

ADVANTAGE - The combination of the **immunostimulatory** nucleic acids and the cancer medicament is synergistic. The combination allows for the administration of higher doses of cancer medicaments without as many side effects, and allows for the administration of lower, sub-therapeutic doses of either compound, but with higher efficacy than would otherwise be achieved using such low doses. The **immunostimulatory** nucleic acids function by enhancement of anti-body dependent cell cytotoxicity. This mechanism provides long lasting effects of nucleic acids, thus reducing dosing regimens, improving compliance and maintenance therapy, reducing emergency situations and improving quality of life.

Dwg.0/0

L8 ANSWER 7 OF 11 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN DUPLICATE 5

AN 2002-665650 [71] WPIDS

DNC C2002-186885

TI Preventing/treating sexually transmitted disease by administering a poly-G **nucleic acid**, a non-motif phosphorothioate **nucleic acid** or a **nucleic acid** to induce an immune response at a local site in the subject.

DC B04 D16

IN **BRATZLER, R L**; PETERSEN, D M

PA (BRAT-I) BRATZLER R L; (PETE-I) PETERSEN D M

CYC 1

PI US 2002091097 A1 20020711 (200271)* 24p

ADT US 2002091097 A1 Provisional US 2000-230637P 20000907, US 2001-949194 20010907

PRAI US 2000-230637P 20000907; US 2001-949194 20010907

AB US2002091097 A UPAB: 20021105

NOVELTY - Preventing or treating (M) a sexually transmitted disease (STD) involves administering to a subject, a poly-G **nucleic acid**, a non-motif phosphorothioate **nucleic acid** or a **nucleic acid** to induce an immune response at a local site in the subject.

DETAILED DESCRIPTION - (M) involves administering to a subject a poly-G **nucleic acid**, a non-motif phosphorothioate **nucleic acid** or a **nucleic acid** to induce an immune response at a local site in the subject, where the subject is at risk of exposure to the local site to an agent that causes STD, such as Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum, Haemophilus ducreyi, Condyloma acuminata, Calymmatobacterium granulomatis, Ureaplasma urealyticum, human T lymphotropic virus type I (HTLV-I), human papilloma virus (multiple types), molluscum contagiosum virus, Trichomonas vaginalis, Phthirus pubis, Candida albicans, Mycoplasma hominis, Gardnerella vaginalis, group B Streptococcus, HTLV-II, hepatitis A, B, C and D viruses, Epstein-Barr virus (EBV), Sarcoptes scabiei, Shigella spp., Campylobacter spp., Giardia lamblia, and Entamoeba histolytica; especially a poly-G **nucleic acid**, where subject is not actively exposed to an antigen and is at risk of exposure at the local site to an agent such as herpes simplex virus type 1 and 2 (HSV1 and HSV2), human papilloma virus (multiple types), HCV, HDV, EBV; especially a non-motif phosphorothioate **nucleic acid**, where subject is at a risk of exposure to human immunodeficiency viruses (HIV-1 and HIV-2), EBV, and cytomegalovirus.

INDEPENDENT CLAIMS are also included for the following:
(1) a non-vaccine composition (I) comprising a **CpG nucleic acid** formulated in a sustained release device in an effective amount, where the **nucleic acid** does not encode a peptide or polypeptide;
(2) a composition (II) comprising a **nucleic acid** such as poly-G **nucleic acid** and a non-motif phosphorothioate **nucleic acid**, formulated in a sustained release device in an effective amount;
(3) a composition (III) comprising a **nucleic acid** ; and a birth control agent, or a birth control device, or an intravenous bag, where the **nucleic acid** is situated within the intravenous bag, or a diaper, where the **nucleic acid** is contained within or on the surface of the diaper; and
(4) a kit (IV) comprising the above compositions, and instructions for administering the composition to a subject having or at risk of developing STD.
ACTIVITY - Antibacterial; Virucide; Anti-HIV; Hepatotropic; Antiinflammatory; Protozoacide; Fungicide; Cytostatic; Antiallergic; Dermatological; Antiarthritic; Antiulcer.
MECHANISM OF ACTION - Inducer of immune response. Test details are described but no results are given.
USE - (M), (I), (II) and (III) are useful for treating or preventing STD caused by the above mentioned viruses, bacteria, protozoa and fungi (claimed), such as AIDS, chancroid, chlamydia, gonorrhoeae, hepatitis, syphilis, trichomonas, venereal warts, pelvic inflammatory disease, pubic lice, scabies, candidiasis, monilial vaginitis and STD-related conditions neoplasias, allergies, acute arthritis, bacterial vaginosis, urethritis, enteritis, enterocolitis, epidymitis, epididymo-or-chitis, Kaposi's sarcoma, gonococcal dermititis, lymphoid neoplasia, mononucleosis syndrome, pharyngitis, proctocolitis, prostatitis, septicemia, tropical spastic paraparesis, ulcerative lesions of the genitalia or squamous cell cancer of the cervis, anus, vulva or penis.
Dwg.0/0

L8 ANSWER 8 OF 11 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN DUPLICATE 6
AN 2001-290487 [30] WPIDS
DNC C2001-088963
TI Improving the efficacy of treatments involving the administration of interferon-alpha by co-administering an isolated **immunostimulatory nucleic acid**.
DC B04 D16
IN **BRATZLER, R L**; HARTMANN, G; KRIEG, A; KRIEG, A M
PA (COLE-N) COLEY PHARM GROUP INC; (IOWA) UNIV IOWA RES FOUND; (COLE-N) COLEY PHARM GMBH
CYC 94
PI WO 2001022990 A2 20010405 (200130)* EN 166p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000076190 A 20010430 (200142)
EP 1220684 A2 20020710 (200253) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2003510290 W 20030318 (200321) 197p
ZA 2002001959 A 20030528 (200341) 178p
ADT WO 2001022990 A2 WO 2000-US26527 20000927; AU 2000076190 A AU 2000-76190 20000927; EP 1220684 A2 EP 2000-965477 20000927, WO 2000-US26527 20000927; JP 2003510290 W WO 2000-US26527 20000927, JP 2001-526199 20000927; ZA 2002001959 A ZA 2002-1959 20020308
FDT AU 2000076190 A Based on WO 2001022990; EP 1220684 A2 Based on WO

2001022990; JP 2003510290 W Based on WO 2001022990
PRAI US 1999-156147P 19990927
AB WO 200122990 A UPAB: 20010603
NOVELTY - Methods for improving the efficacy (e.g. reducing the dosage required and/or side effects) of treatments involving the administration of interferon (IFN)- alpha , comprising co-administering the IFN- alpha with an isolated **immunostimulatory nucleic acid** (INA), are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a method (I) of administering interferon (IFN)- alpha , comprising administering an isolated **immunostimulatory nucleic acid** (INA);

(2) a method (II) of supplementing IFN- alpha treatment comprising administering to a subject in need of IFN- alpha treatment, IFN- alpha and an isolated INA;

(3) a method (III) of treating a subject to activate interferon-producing cells (IPC) of a subject, comprising:

(a) isolating IPCs from a subject in need of treatment;

(b) culturing the IPCs in vitro;

(c) contacting the IPCs in vitro with an isolated INA; and

(d) returning the contacted IPCs to the subject;

(4) a method (IV) of increasing efficacy of IFN- alpha treatment of a subject, comprising:

(a) administering to a subject a composition comprising IFN- alpha ; and

(b) co-administering to the subject a composition comprising an INA which, together with the IFN- alpha , is an effective IFN- alpha treatment (the efficacy of the IFN- alpha treatment is greater than the efficacy of administering the same amount of IFN- alpha in the absence of the INA);

(5) a method (V) of decreasing a dose of an IFN- alpha effective for treating a subject, comprising:

(a) administering to a subject a composition comprising IFN- alpha ;

(b) co-administering to the subject a composition comprising an INA which, together with the IFN- alpha , is an effective IFN- alpha treatment (the amount of the IFN- alpha administered is less than the amount required in the absence of the INA);

(6) a method (VI) of preventing an IFN- alpha treatment-related side effect in a subject undergoing treatment with IFN- alpha , comprising:

(a) administering to a subject in need of treatment a composition comprising IFN- alpha s; and

(b) co-administering to the subject a composition comprising an INA which together with the IFN- alpha is an effective IFN- alpha treatment (an IFN- alpha related side effect is reduced in comparison to the side effect when IFN- alpha s is administered in the absence of co-administering the INA);

(7) a method (VII) of enhancing efficacy of IFN- alpha treatment in a subject, comprising:

(a) administering to a subject in need of treatment, a composition comprising IFN- alpha for treating a disorder in the subject;

(b) isolating natural interferon-producing cells (IPCs) from a donor;

(c) contacting he isolated IPCs ex vivo with a composition comprising an INA for inducing the IPCs to release IFN- alpha ; and

(d) administering the contacted cells to the subject;

(8) a method (VIII) of supporting survival of natural interferon-producing cells (IPCs) in vitro, comprising:

(a) isolating IPCs from a subject;

(b) culturing the IPCs in a sterile medium suitable for tissue culture; and

(c) contacting the IPCs in vitro with an INA which supports the growth of the IPCs in the absence of interleukin (IL)-3;

(9) a method (IX) of stimulating isolated interferon-producing cells (IPCs) in vitro, comprising:

(a) isolating IPCs from a subject;

(b) culturing the IPCs in a sterile medium suitable for tissue culture; and

(c) contacting the IPCs in vitro with an INA to induce secretion of at least 1 type 1 interferon;

(10) a method (X) of stimulating production of a number of type 1 IFN subtypes, comprising contacting IPCs with an INA to induce secretion of at least 2 type 1 IFNs;

(11) a method (XI) of inhibiting IL-12 production, comprising contacting IL-12 producing cells, in the presence of interferon-producing cells conditions in which the IL-12 producing cells normally produce IL-12, with an INA that induces secretion of type 1 IFN;

(12) an isolated nucleic acid comprising one of 37 defined nucleotide sequences ((N1)-(N37)) given in the specification; and

(13) a composition comprising (XI) and IFN- alpha .

USE - Methods for improving the efficacy (e.g. reducing the dosage required and/or side effect) of treatments involving the administration of interferon (IFN)- alpha to a subject. The subject is suffering from a proliferative disorder (e.g. hairy cell leukemia, chronic myelogenous leukemia, cutaneous T-cell leukemia, multiple myeloma, follicular lymphoma, malignant melanoma, squamous cell carcinoma, AIDS (acquired immunodeficiency syndrome)-related Kaposi's sarcoma, renal cell carcinoma, prostate carcinoma, bladder cell carcinoma, cervical dysplasia and/or colon carcinoma) and/or a viral infection (e.g. hepatitis B, hepatitis C, condyloma acuminatum, human immunodeficiency virus, herpes, cytomegalovirus, Epstein-Barr virus and/or papillomavirus).

ADVANTAGE - The administration of the INA improves the efficacy of the IFN- alpha therapy, e.g. by reducing the side effects associated with IFN- alpha administration.

Dwg.0/18

L8 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 7
AN 1977:202832 BIOSIS
DN BA64:25196
TI **NUCLEIC-ACID** RELATED COMPOUNDS PART 25 SYNTHESES OF ARABINO XYLO AND LYXO ANHYDRO SUGAR NUCLEOSIDES FROM TUBERCIDIN RIBO EPOXIDE.
AU ROBINS M J; **FOURON Y**; MUHS W H
SO CAN J CHEM, (1977) 55 (7), 1260-1267.
CODEN: CJCHAG. ISSN: 0008-4042.
FS BA; OLD
LA Unavailable
AB Treatment of the trans iodohydrin acetate, 4-amino-7-(3-iodo-3-deoxy-2-O-acetyl-5-O-[2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl]-.beta.-D-xylofuranosyl)pyrrolo[2,3-d]pyrimidine with methanolic ammonia gave 2',3'-anhydrotubercidin (3) in 96% yield. N4,N4,O5'-Tribenzoylation of 3 gave 4, which is stabilized against intramolecular cyclization. Treatment of 4 with boron trifluoride etherate (3',5'-benzoxonium ion formation) followed by deblocking gave 4-amino-7-.beta.-D-xylofuranosylpyrrolo[2,3-d]pyrimidine (5) in 91% overall yield from tubercidin. The 3',5'-O-isopropylidene derivative (6a) of 5 was mesylated to give 6b which was deprotected in acid and the resulting trans hydroxy mesylate was treated with base to give 4-amino-7-(2,3-anhydro-.beta.-D-lyxofuranosyl)pyrrolo[2,3-d]pyrimidine. This lyxo epoxide was treated with sodium benzoate to give 4-amino-7-.beta.-D-arabinofuranosylpyrrolo[2,3-d]pyrimidine. Biochemical, spectroscopic and chemical properties of these semisynthetic antibiotic analogues of biologically active adenine nucleosides are discussed.

L8 ANSWER 10 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 8
AN 1977:159809 BIOSIS
DN BA63:54673
TI **NUCLEIC-ACID** RELATED COMPOUNDS PART 22 TRANSFORMATION

OF RIBO NUCLEOSIDE 2 3-O ORTHO ESTERS INTO HALO SUGAR NUCLEOSIDES DEOXY SUGAR NUCLEOSIDES AND EPOXY SUGAR NUCLEOSIDES USING ACYL HALIDES MECHANISM AND STRUCTURE OF PRODUCTS.

AU ROBINS M J; MENGEL R; JONES R A; **FOURON Y**

SO J AM CHEM SOC, (1976) 98 (25), 8204-8213.
CODEN: JACSAT. ISSN: 0002-7863.

FS BA; OLD

LA Unavailable

AB Treatment of 2',3'-O-methoxyethylideneadenosine (2) with pivalic acid chloride in refluxing pyridine gave an unresolved mixture of 6-N-pivalamido-9-(3-chloro-3-deoxy-2-O-acetyl-5-O-pivalyl-.beta.-D-xylofuranosyl)purine (4a) and its 2'-chloroarabino isomer (3a) as the major product. 6-N-pivalamido-9-(3-chloro-3-deoxy-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-.beta.-D-xylofuranosyl)purine (4b) and its 2'-chloroarabino isomer (3b) were produced by acylation reactions involving a 2',3'-O-ketene acetal (11) which is in equilibrium with the initially formed 2',3'-acetoxonium ion intermediate (10). The structure of the complex 4,4-dimethyl-3-pivaloxypent-2-enoate (DMPP) group was deduced by NMR and mass spectroscopy and verified by synthesis of ethyl DMPP (9) from ethyl orthoacetate and pivalyl chloride/NaI. Treatment of 2 with pivalyl chloride and excess NaI in refluxing pyridine gave the corresponding 3'-iodoxylo and 2'-iodoarabino DMPP-blocked nucleosides (4c and 3c) in good combined yield accompanied by unsaturated products. The absence of the corresponding acetyl iodo derivatives was rationalized on the basis of greater acylating activity of pivalyl iodide (generated in situ) in the postulated mechanistic sequence involving ketene acetal intermediates. A pivalylketene acetal derivative (14) was isolated and converted to 3c and 4c under the reaction conditions. Treatment of 3a,4a with tri-n-butyltin hydride or of 3c and 4c under catalytic hydrogenolysis conditions gave 2'-deoxyadenosine (7) and 3'-deoxyadenosine (cordycepin) (8), respectively, after deblocking. The ribo epoxide, 9-(2,3-anhydro-.beta.-D-ribofuranosyl)adenine (6), was formed on treatment of 3a-c and 4a-c with methanolic sodium methoxide. This proved the 2',3'-trans orientation of halo and acyloxy substituents and provides convenient access to the synthetically useful 6. Spectroscopic identification of products, the acyloxonium ion mediated mechanism and comparison of the route with previously reported procedures are discussed.

L8 ANSWER 11 OF 11 MEDLINE on STN DUPLICATE 9

AN 74174718 MEDLINE

DN 74174718 PubMed ID: 4833508

TI **Nucleic acid** related compounds. 11. Adenosine 2',3'-ribo-epoxide. Synthesis, intramolecular degradation, and transformation into 3'-substituted xylofuranosyl nucleosides and the lyxo-epoxide.

AU Robins M J; **Fouron Y**; Mengel R

SO JOURNAL OF ORGANIC CHEMISTRY, (1974 May 31) 39 (11) 1564-70.
Journal code: 2985193R. ISSN: 0022-3263.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 197407

ED Entered STN: 19900310
Last Updated on STN: 19900310
Entered Medline: 19740731

=> s asthma or allergy
L9 418622 ASTHMA OR ALLERGY

=> s cpg or nucleic acid (5a) adjuvant
L10 29905 CPG OR NUCLEIC ACID (5A) ADJUVANT

oligodeoxynucleotides (ODNs) were able to induce B cell proliferation and to shift the in vitro differentiation of Dermatophagoides pteronyssinus group 1-specific human CD4+ T cells from atopic donors into Th cell effectors showing a prevalent Th1, instead of Th2, cytokine profile. This latter effect was completely blocked by the neutralization of IL-12 and IFN (.alpha. and .gamma.) in bulk culture, suggesting that the Th1-inducing activity of **phosphorothioate** ODNs was mediated by their ability to stimulate the production of these cytokines by monocytes, dendritic, and NK cells. Cytosine methylation abolished the Th1-inducing activity of ODNs; however, **CpG** dinucleotide-containing ODNs exhibited the Th1-shifting effect independently of the presence or the absence of **CpG** motifs (5'-pur-pur-**CpG**-pyr-pyr-3'). Moreover, the inversion of **CpG** to GpC resulted only in a partial reduction of this activity, suggesting that the motif responsible for the Th1-skewing effect in humans is at least partially different from that previously defined in mice. These results support the concept that the injection of allergens mixed to, or conjugated with, appropriate ODNs may provide a novel allergen-specific immunotherapeutic regimen for the treatment of allergic disorders.

L19 ANSWER 4 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2003-493178 [46] WPIDS
DNC C2003-131980
TI Immunostimulatory oligonucleotides for use in treating cancer, skin disorders, **asthma**, **allergy**, comprises two oligonucleotides linked at their 3' ends, a nucleobase or sugar by a non-nucleotidic linker.
DC B04 D16
IN AGRAWAL, S; BHAGAT, L; KANDIMALLA, E R; YU, D
PA (HYBR-N) HYBRIDON INC
CYC 89
PI WO 2003035836 A2 20030501 (200346)* EN 96p
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
ADT WO 2003035836 A2 WO 2002-US33756 20021022
PRAI US 2001-344767P 20011024
AB WO2003035836 A UPAB: 20030719
NOVELTY - An immunomer comprising at least two oligonucleotides linked at their 3' ends, or internucleoside linkages or a functionalized nucleobase or sugar by a non-nucleotidic linker, where at least one of the oligonucleotides is an immunostimulatory oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an immunomer conjugate comprising the above immunomer, and an antigen conjugated to the immunomer at a position other than the accessible 5' end; and

(2) a pharmaceutical formulation comprising the above immunomer.

ACTIVITY - Cytostatic; Immunosuppressive; Antibacterial; Virucide; Antiparasitic; Antiinflammatory; Antiallergic; Antiasthmatic; Dermatological.

No biological data given.

MECHANISM OF ACTION - Vaccine; Stimulator of immune response.

To test the effect on immunostimulatory activity of **CpG** DNA containing branched alkyl-linkers, two branched alkyl-linkers containing a hydroxyl or an amine functional group were incorporated into parent **CpG** DNA (CTATCTGACGTTCTCTGT) and the effects on immunostimulatory activity of the resulting modified **CpG** DNAs (CTATCTGCGTTCTCTGT, CTATCTACGTTCTCTGT, CTACTGACGTTCTCTGT) were examined. The data obtained with modified **CpG** DNAs containing aminolinkers at different

nucleotide positions, in BALB/c mouse spleen cell cultures (proliferation) and in vivo (splenomegaly) showed that the **CpG** DNA containing an aminobutyryl propanediol-linker induced spleen cell proliferation in BALB/c mice spleen cell cultures and splenomegaly in BALB/c mice. Parent **CpG** DNA showed a proliferation index of 3.7 plus or minus 0.8 at a concentration of 0.1 micro g/ml. At the same concentration, modified **CpG** DNAs containing amino-linker at different positions caused higher spleen cell proliferation than did the parent **CpG** DNA. As observed with other linkers, when the substitution was placed adjacent to **CpG** dinucleotide, a lower proliferation index was noted compared with parent **CpG** DNA, further confirming that the placement of a linker substitution adjacent to **CpG** dinucleotide had a detrimental effect on immunostimulatory activity. In general, substitution of an amino-linker for 2'-deoxyribonucleoside in the 5'-flanking sequence resulted in higher spleen cell proliferation than found with the substitution in the 3' flanking sequence. Similar results were observed in the splenomegaly assay, confirming the results observed in spleen cell cultures. Modified **CpG** DNAs containing glycerol-linker showed immunostimulatory activity similar to or slightly higher than that observed with modified **CpG** DNA containing an amino-linker.

USE - The immunomer and the immunomer conjugate are useful for generating an immune response in a vertebrate and also for treating a patient having a disease or disorder, such as cancer, autoimmune disorder, airway inflammation, inflammatory disorders, skin disorders, **allergy**, **asthma** or a disease caused by a pathogen. The method comprises administering a vaccine, where the vaccine and immunomer are linked to an immunogenic protein, and further administering an adjuvant (claimed). The immunomer is useful for treating autoimmune disorders, bacteria, parasitic and viral infections in adult and pediatric human and veterinary applications. The immunomers are also useful as adjuvants in combination with DNA vaccines, antibodies, allergens, chemotherapeutic agents and antisense oligonucleotides.

Dwg.0/21

L19 ANSWER 5 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2002-689667 [74] WPIDS
CR 1996-105847 [11]; 1998-272127 [24]; 2000-086224 [07]; 2001-217934 [22]; 2001-280761 [29]; 2001-380456 [40]; 2003-466135 [44]; 2003-512356 [48]
DNC C2002-194884
TI Activating a dendritic cell for cancer immunotherapy or for treating infectious or **allergy** disease, by contacting a dendritic cell with an isolated nucleic acid containing at least one unmethylated **CpG** dinucleotide.
DC B04 D16
IN HARTMANN, G; KRIEG, A M
PA (IOWA) UNIV IOWA RES FOUND
CYC 1
PI US 6429199 B1 20020806 (200274)* 52p
ADT US 6429199 B1 CIP of US 1994-276358 19940715, CIP of US 1995-386063 19950207, CIP of US 1996-738652 19961030, CIP of US 1997-960774 19971030, US 1998-191170 19981113
FDT US 6429199 B1 CIP of US 6194388, CIP of US 6207646, CIP of US 6239116
PRAI US 1998-191170 19981113; US 1994-276358 19940715; US 1995-386063 19950207; US 1996-738652 19961030; US 1997-960774 19971030
AB US 6429199 B UPAB: 20030729

NOVELTY - Activating (M) or causing maturation of a dendritic cell, comprising contacting a dendritic cell with an isolated nucleic acid containing at least one unmethylated **CpG** dinucleotide, where the nucleic acid is from 8-80 bases in length in an amount effective to activate or cause maturation of the dendritic cell, where the activation is performed ex vivo, is new.

ACTIVITY - Cytostatic; Antiallergic.

MECHANISM OF ACTION - Activator of dendritic cells (claimed); Inducer of dendritic cell maturation.

Mature human dendritic cell (DC) expressed the specific DC marker CD83, while immature DC do not. Mature DC effectively presented antigen and maintained their stimulatory capacity while migrating from peripheral tissues to lymph nodes. Maturation of DC was thought to be essential if these cells were intended to be used for therapeutic strategies where they would be activated ex vivo, pulsed with antigens, and then reinfused into a patient. Freshly isolated DC were incubated for 3 days with granulocyte macrophage-colony stimulating factor (GM-CSF), lipopolysaccharide (LPS) or oligonucleotides. The results showed that in the absence of either GM-CSF or **CpG**, or with the methylated control oligonucleotide 2117: 5'-TQGTQGTTTTGTQGTTTTGTQGTT-3' (2 micro g/ml), survival of cells was poor. The remaining viable cells did not express CD83. Cells incubated with GM-CSF showed low expression of CD86, and only 4.1 % of the cells expressed CD83. If LPS was present in addition to GM-CSF, the percentage of CD83 positive cells was increased to 8.6 %. In contrast, the single addition of the **CpG** oligonucleotide 2006: 5'-TCGTCGTTTTGTCGTTTTGTCGTT-3' rendered 16 % of the DC CD83 positive. The combination of GM-CSF and 2006 enhanced CD83 expression synergistically (37 %). This induction of CD83 expression was **CpG** specific as showed by the control oligonucleotide 2117 in combination with GM-CSF (9.7 %).

USE - (M) is useful for cancer immunotherapy or for treating an infectious disease or **allergy**, by administering an activated dendritic cell that express a specific cancer, microbial or **allergy** causing antigen, to a subject having a cancer including the cancer antigen, to a subject having an infection with a microorganism including the microbial antigen or to a subject having an allergic reaction to the **allergy** causing antigen, where the activated dendritic cell is prepared by (M). (M) is useful for generating a high yield of dendritic cells by administering an isolated nucleic acid containing at least one unmethylated **CpG** dinucleotide, where the nucleic acid is 8-80 bases in length in an amount effective to activate the dendritic cells to a subject, and isolating dendritic cells from the subject. (All claimed).

ADVANTAGE - The use of **CpG** allows the generation of mature dendritic cells from peripheral blood within two days in a well defined system. The application of **CpG** for this purpose is superior to granulocyte macrophage-colony stimulating factor (GM-CSF), which is currently used for this purpose. **CpG** oligonucleotides have a longer half life, are less expensive, and show a greater magnitude of immune effects.

Dwg.2/12

L19 ANSWER 6 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2002-527359 [56] WPIDS
DNC C2002-149289
TI Method for modulating the immunostimulatory effect of an immunostimulatory oligonucleotide compound, and new immunostimulatory oligonucleotide compounds.
DC B02 D16
IN AGRAWAL, S; KANDIMALLA, E R; YU, D; ZHAO, Q
PA (HYBR-N) HYBRIDON INC; (AGRA-I) AGRAWAL S; (KAND-I) KANDIMALLA E R; (YUDD-I) YU D; (ZHAO-I) ZHAO Q
CYC 96
PI WO 2002026757 A2 20020404 (200256)* EN 94p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001094750 A 20020408 (200256)
US 2002137714 A1 20020926 (200265)
EP 1322656 A2 20030702 (200344) EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR

ADT WO 2002026757 A2 WO 2001-US30137 20010926; AU 2001094750 A AU 2001-94750 20010926; US 2002137714 A1 Provisional US 2000-235452P 20000926, Provisional US 2000-235453P 20000926, CIP of US 2000-712898 20001115, US 2001-965116 20010926; EP 1322656 A2 EP 2001-975423 20010926, WO 2001-US30137 20010926

FDT AU 2001094750 A Based on WO 2002026757; EP 1322656 A2 Based on WO 2002026757

PRAI US 2000-712898 20001115; US 2000-235452P 20000926; US 2000-235453P 20000926; US 2001-965116 20010926

AB WO 200226757 A UPAB: 20020903

NOVELTY - Positional chemical modifications introduced in immunostimulatory oligonucleotide compounds affect their immunostimulatory capabilities. New imunostimulatory oligonucleotide compounds are claimed.

DETAILED DESCRIPTION - A method for modulating the immunostimulatory effect of an immunostimulatory oligonucleotide compound comprises:

(a) introducing into the immunostimulatory domain a dinucleotide analog that includes a non-naturally occurring pyrimidine base;

(b) introducing into the immunostimulatory domain and/or potentiation domain an immunostimulatory moiety; or

(c) introducing into the oligonucleotide a 3'-3' linkage.

INDEPENDENT CLAIMS are included for the following:

(1) new immunostimulatory oligonucleotide compounds comprising:

(a) an immunostimulatory dinucleotide of formula 5'-pyrimidine purine-3', where pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural or non-natural purine nucleoside;

(b) an immunostimulatory dinucleotide of formula C asterisk pG;

(c) immunostimulatory domains of formula 5'------X1-X2-Y-Z X3-X4------3' (II);

(d) a sequence of formula 5'-Um..U1-X1-X2-Y-Z-X3-X4D1.m 3' (III) and

(2) a method of generating an immune response comprising administering an oligonucleotide analog described in (1).

C asterisk = a cytidine analog;

G = guanosine, 2'-deoxyguanosine or a guanosine analog;

p = an internucleotide linkage selected from phosphodiester, **phosphorothioate** and phosporodithioate;

Y = cytidine, 2'-deoxycytidine, or a non-natural pyrimidine nucleoside;

Z = guanosine, 2'-deoxyguanosine, or a non-natural purine nucleoside;

X1 = a naturally occurring nucleoside or an immunostimulatory moiety selected from a 3C alkyl linker, 2 aminobutyl-1,3-propanediol linker, and beta -L-deoxynucleoside;

X2 = a naturally occurring nucleoside or an immunostimulatory moiety that is an amino linker;

X3 = a naturally occurring nucleoside or an immunostimulatory moiety that is a nucleoside methylphosphonate;

X4 = a naturally occurring nucleoside or an immunostimulatory moiety selected from nucleoside methylphosphonate and 2'-O-methylribonucleoside;

Y = a non-natural pyrimidine nucleoside;

Z = guanosine, 2' deoxy-guanosine or a non-natural purine nucleoside;

X = a naturally occurring nucleoside or an immunostimulatory moiety;

Um-U1 = an upstream potentiation domain where each U is a naturally occurring nucleoside or an immunostimulatory moiety;

D1-Dm = a downstream potentiation domain where each D is a naturally occurring nucleoside or an immunostimulatory moiety; and

m = 0-30.

With the proviso that at least 1 of X1-X4 is an immunostimulatory moiety.

ACTIVITY - Immunostimulatory; Antiviral; Antibacterial; Antiparasitic; Cytostatic; Anitallergic; Antiasthmatic; Respiratory.

The immunostimulatory activity of end-blocked CpG-PS-oligos was

studied in a lymphocyte proliferation assay. Mouse spleen lymphocytes were cultured with CpG-PS-oligos at 0.1, 1 and 10 micro g/ml for 48 hours and cell proliferation was determined by 3H uridine incorporation.

Oligo A induced a dose-dependent effect on cell proliferation (proliferation index (PI) 5.0 plus or minus 0.32 at 10 micro g/ml). Oligo B, which consisted of 2 units of A linked by a 3'-5'-linkage, had PI 5.8 plus or minus 0.28 at the same dose. Oligo C, which consisted of 2 units of A linked by a 5'-5'-linkage, had PI 2.0 plus or minus 0.26, showing a significantly lower immunostimulatory activity than observed for A or B. Oligo D, which consisted of 2 units of A linked by a 3'-3' linkage, had PI 7.2 plus or minus 0.5, showing a greater immunostimulatory activity than observed for A or B.

MECHANISM OF ACTION - None given in the source material.

USE - For treating a disease caused by a pathogen, e.g. a virus, parasite or bacterium; cancer; autoimmune disorders (e.g. autoimmune asthma); or airway inflammation or allergy.

The oligonucleotide may be administered in combination with an antibiotic, antigen, allergen, vaccine, antibody, cytotoxic agent, antisense oligonucleotide, gene therapy vector, DNA vaccine or adjuvant, particularly with a chemotherapeutic compound in the treatment of cancer.
Dwg.0/28

L19 ANSWER 7 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2002-130570 [17] WPIDS
DNC C2002-040090
TI New immunostimulatory compositions comprising RNA/DNA hybrid oligonucleotides, useful for enhancing an immune response or inducing cytokines, particularly for treating diseases, e.g. cancer, **allergy** or HIV infection.
DC B04 D16
IN FLORA, M; KLINMAN, D M; MOND, J J
PA (BIOS-N) BIOSYNEXUS INC
CYC 96
PI WO 2001093902 A2 20011213 (200217)* EN 68p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001075294 A 20011217 (200225)
EP 1292331 A2 20030319 (200322) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2001093902 A2 WO 2001-US18276 20010607; AU 2001075294 A AU 2001-75294 20010607; EP 1292331 A2 EP 2001-941989 20010607, WO 2001-US18276 20010607
FDT AU 2001075294 A Based on WO 2001093902; EP 1292331 A2 Based on WO 2001093902
PRAI US 2000-209797P 20000607
AB WO 200193902 A UPAB: 20020313
NOVELTY - An immunostimulatory composition, which comprises at least one oligonucleotide comprising both an RNA region and a DNA region, is new. At least one terminus of the oligonucleotide comprises RNA.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an adjuvant comprising the immunostimulatory composition;

(2) vaccines (I) comprising:

(a) at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA, where the oligonucleotide is associated with a physiological carrier or delivery system;

(b) at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA, and at least one target antigen;

(3) a method of stimulating innate immunity comprising administering at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA, and where the oligonucleotide is associated with a physiological carrier or delivery system;

(4) a method of stimulating global immunity comprising administering at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA, and where the oligonucleotide is associated with a physiological carrier or delivery system;

(5) methods of stimulating a cellular immune response or a humoral immune response comprising administering the vaccine of (Ib); and

(6) a method of making a vaccine comprising associating:

(a) at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA; and

(b) a physiological carrier or delivery system.

ACTIVITY - Immunostimulant; antiallergic; cytostatic; antimicrobial; immunosuppressive; anti-HIV; protozoacide; virucide; hepatotropic; antiinflammatory; antibacterial.

MECHANISM OF ACTION - Gene therapy; cytokine stimulator; vaccine. The stimulation of cytokines interleukin-6 (IL-6) and interferon gamma (IFN-gamma) in human peripheral lymphocytes cultured from four healthy volunteer subjects, designated S1 through S4, was assayed using standard methods. Oligonucleotides DDD and RDR were added to the media of cultured cells to final concentrations of 0.3, 3, or 30 micro g/ml. 24 hours after oligonucleotide addition, Th1 and Th2-type cytokine levels in the media were determined by enzyme linked immunoabsorbant assay (ELISA). The hybrid DNA/RNA oligonucleotides stimulated the production of cytokines implicated in eliciting both Th1 (IFN- gamma) and Th2 T (IL-6) type responses in human peripheral lymphocytes. At the highest concentrations tested, for example, the hybrid RDR molecule was 3-fold more effective at inducing IFN- gamma and 5-fold more effective at stimulating the release of IL-6.

USE - The composition is useful for enhancing an immune response or inducing cytokines. The compositions comprising the oligonucleotides are useful as vaccine adjuvants and in treating diseases, e.g. pathogenic infection, (non-)malignant tumors (e.g. cancers of the brain, lung, ovary, breast, prostate or colon, or carcinomas and sarcomas), autoimmune disease or **allergy** (e.g. allergic rhinitis, hay fever or food allergies), lyme disease, hepatitis, HIV or malaria. The composition is also useful for treating, preventing or ameliorating the symptoms resulting from exposure to a bio-warfare agent, e.g. Ebola, Anthrax or Listeria.

Dwg.0/0

L19 ANSWER 8 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2001-273485 [28] WPIDS
DNC C2001-082927
TI Vaccinating against tumors, infectious diseases, allergies and **asthma** using immunostimulatory Py-rich and TG nucleic acids.
DC B04 D16
IN KRIEG, A M; SCHETTER, C; VOLLMER, J; KRIEG, A
PA (COLE-N) COLEY PHARM GMBH; (IOWA) UNIV IOWA RES FOUND
CYC 88
PI WO 2001022972 A2 20010405 (200128)* EN 336p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
AU 2000076153 A 20010430 (200142)
NO 2002001453 A 20020527 (200247)
EP 1221955 A2 20020717 (200254) EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

BR 2000014236 A 20021015 (200276)
HU 2002002639 B 20021228 (200308)
CZ 2002001050 A3 20030115 (200309)
KR 2002068509 A 20020827 (200309)
JP 2003510282 W 20030318 (200321) 423p
SK 2002000396 A3 20030401 (200331)
ZA 2002001963 A 20030528 (200341) 378p

ADT WO 2001022972 A2 WO 2000-US26383 20000925; AU 2000076153 A AU 2000-76153 20000925; NO 2002001453 A WO 2000-US26383 20000925, NO 2002-1453 20020322; EP 1221955 A2 EP 2000-965433 20000925, WO 2000-US26383 20000925; BR 2000014236 A BR 2000-14236 20000925, WO 2000-US26383 20000925; HU 2002002639 B WO 2000-US26383 20000925, HU 2002-2639 20000925; CZ 2002001050 A3 WO 2000-US26383 20000925, CZ 2002-1050 20000925; KR 2002068509 A KR 2002-703845 20020323; JP 2003510282 W WO 2000-US26383 20000925, JP 2001-526182 20000925; SK 2002000396 A3 WO 2000-US26383 20000925, SK 2002-396 20000925; ZA 2002001963 A ZA 2002-1963 20020308

FDT AU 2000076153 A Based on WO 2001022972; EP 1221955 A2 Based on WO 2001022972; BR 2000014236 A Based on WO 2001022972; HU 2002002639 B Based on WO 2001022972; CZ 2002001050 A3 Based on WO 2001022972; JP 2003510282 W Based on WO 2001022972; SK 2002000396 A3 Based on WO 2001022972

PRAI US 2000-227436P 20000823; US 1999-156113P 19990925; US 1999-156135P 19990927

AB WO 200122972 A UPAB: 20010522

NOVELTY - A method (I) of stimulating an immune response, comprising administering an immunostimulatory nucleic acid (INA) (selected from a Py-rich nucleic acid and a TG nucleic acid) to a non-rodent subject in sufficient quantity to stimulate an immune response, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a composition (II) comprising a sustained release device including an INA, which is free of unmethylated **CpG** motifs (and is selected from a T-rich nucleic acid and a TG nucleic acid);

(2) a composition (III) comprising an INA which is free of unmethylated **CpG** motifs (and is selected from a T-rich nucleic acid and a TG nucleic acid) and an antigen;

(3) a composition (IV) comprising an INA which is free of unmethylated **CpG** motifs (and is selected from a T-rich nucleic acid and a TG nucleic acid) and an antimicrobial agent;

(4) a composition (V) comprising an INA and an anti-cancer therapy for treating cancers or to reduce the risk of developing a cancer (the INA is selected from a T-rich nucleic acid and a TG nucleic acid);

(5) a composition (VI) comprising an immunostimulatory nucleic acid and/or an **asthma/allergy** treatment for preventing or treating an immune response associated with exposure to a mediator of **asthma** or **allergy** (the INA is selected from a T-rich nucleic acid, a TG nucleic acid and/or a C-rich nucleic acid);

(6) a composition (VII) comprising an INA selected from 4661 defined nucleic acid sequences given in the specification;

(7) a composition (VIII) an INA comprising (S5) (in which 1 of the Cs is unmethylated and the INA has less than 100 nucleotides); and

(8) a composition (IX) comprising an INA comprising (S6) (in which 1 of the Cs is unmethylated, the INA has less than 100 nucleotides and a phosphodiester backbone) and a sustained release device.

5'-M1TCGTCGTTM2-3' (S5)

M1 = a nucleic acid with at least 1 nucleotide; and

M2 = a nucleic acid having 0-50 nucleotides.

5'-TCGTCGTT-3' (S6)

ACTIVITY - Cytostatic; virucidal; bactericidal; fungicidal; anti-parasitic; immunostimulatory.

MECHANISM OF ACTION - Vaccine.

USE - The method is used to vaccinate subjects such as humans, dogs, cats, horses, cows, pigs, sheep, goats, chickens, monkeys or fish against

tumor antigens, viral antigens (e.g. herpesviridae, retroviridae and/or orthomyxoviridae), bacterial antigens (e.g. toxoplasma, haemophilus, campylobacter, clostridium, Escherichia coli and/or staphylococcus), fungal antigens and/or parasitic antigens. The subject has or is at risk of developing cancer (especially), **asthma**, infectious disease and/or an **allergy** and the method is used for preventing that cancer, **asthma**, disease or **allergy**. The cancer is biliary tract cancer, brain cancer, breast cancer, cervical cancer, choriocarcinoma, brain or central nervous system (CNS) cancer, colon cancer, connective tissue cancer, endometrial cancer, eye cancer, gastric cancer, intraepithelial neoplasms, esophageal cancer, eye cancer larynx cancer, lymphomas, Hodgkin's lymphoma, liver cancer, lung cancer (e.g. small cell and non-small cell), melanoma, neuroblastoma, oral cavity cancer, ovarian cancer, pancreas cancer, prostate cancer, rectal cancer, sarcomas, thyroid cancer, bone cancer, skin cancer, testicular cancer and/or renal cancer (claimed).
Dwg.0/12

L19 ANSWER 9 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2000-679539 [66] WPIDS
DNC C2000-206683
TI Low adenosine (A) content antisense oligonucleotides which do not trigger adenosine receptors during metabolism, useful e.g. for treating cancers and respiratory obstructions.
DC B04 D16
IN NYCE, J W; CHEN, E; CHEN, L; FERNANDEZ-DE-CASTRO, J; SAUNDERS, D
PA (NYCE-I) NYCE J W; (UYEC-N) UNIV EAST CAROLINA; (CHEN-I) CHEN E; (CHEN-I) CHEN L; (FERN-I) FERNANDEZ-DE-CASTRO J; (SAUN-I) SAUNDERS D
CYC 86
PI WO 2000062736 A2 20001026 (200066)* EN
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 2000040317 A 20001102 (200107)
BR 2000006019 A 20010313 (200118)
EP 1168919 A2 20020109 (200205) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
US 2001053037 A1 20011220 (200206)
MX 2000012093 A1 20010501 (200227)
CN 1330513 A 20020109 (200229)
KR 2002095600 A 20021228 (200330)
JP 2003515525 W 20030507 (200331)
ADT WO 2000062736 A2 WO 2000-US8020 20000324; AU 2000040317 A AU 2000-40317 20000324; BR 2000006019 A BR 2000-6019 20000324, WO 2000-US8020 20000324; EP 1168919 A2 EP 2000-919668 20000324, WO 2000-US8020 20000324; US 2001053037 A1 Provisional US 1999-127958P 19990406, US 2001-902988 20010711; MX 2000012093 A1 MX 2000-12093 20001206; CN 1330513 A CN 2000-801046 20000324; KR 2002095600 A KR 2000-713847 20001206; JP 2003515525 W JP 2000-611873 20000324, WO 2000-US8020 20000324
FDT AU 2000040317 A Based on WO 2000062736; BR 2000006019 A Based on WO 2000062736; EP 1168919 A2 Based on WO 2000062736; JP 2003515525 W Based on WO 2000062736
PRAI US 1999-127958P 19990406; US 2001-902988 20010711
AB WO 200062736 A UPAB: 20001219
NOVELTY - Low adenosine (A) content antisense oligonucleotides (oligo(s)) and compositions (I) comprising them, are new. In the oligo(s), the A is replaced by a 'Universal' or alternative base.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(1) a pharmaceutical composition (I), comprising an

oligonucleotide(s) (oligo(s)) which is (are) effective for alleviating bronchoconstriction and/or lung inflammation, **allergy**(ies), or surfactant depletion or hyposecretion, when administered to a mammal (the oligo comprises 0-15% adenosine (A) and is antisense to a target selected from the initiation codon, the coding region, the 5'-end and the 3'-end genomic flanking regions, the 5' and 3' intron-exon junctions, and regions within 2 to 10 nucleotides of the junctions of a gene encoding a target polypeptide associated with lung airway dysfunction or anti-sense to the polypeptide mRNA), combinations of the oligos and/or mixtures of the oligos;

(2) a cell, carrying the oligo(s) of (1);

(3) a kit (II), comprising a delivery device, (in a separate container(s)) the oligo(s) of (I) and instructions for adding a carrier and for use of the kit;

(4) an in vivo method of delivering an anti-sense oligonucleotide(s) (oligo(s)) to one or more target polynucleotide(s), comprising administering into the respiratory system of a subject one or more oligo(s) that are anti-sense to the polynucleotide(s), in an amount effective to reach and hybridize to the target polynucleotide(s), and reduce the production or availability, or to increase the degradation, of the target mRNA, or to reduce the amount of the target polypeptide present in the lungs; and

(5) an in vivo method (III) of delivering an anti-sense oligonucleotide (oligo) to a target polynucleotide associated with bronchoconstriction and/or lung inflammation, **allergy**(ies) and/or surfactant hypoproduction, comprising administering to a subject the composition (I)', which comprises an amount of the oligo(s) effective to reach and hybridize to the target polynucleotide(s), and reduce or inhibit the polynucleotide(s)' transcription and/or expression and, therefore, alleviating the bronchoconstriction and/or lung inflammation, **allergy**(ies) and/or surfactant hypoproduction.

ACTIVITY - Respiratory; bronchodilator; antiinflammatory; immunosuppressive; antiasthmatic; analgesic; hypotensive; cytostatic.

MECHANISM OF ACTION - Antisense inhibition of nucleic acid/protein expression.

USE - The oligo(s) may be formulated into compositions (I) and used (III) to down-regulate the expression and or activity of target polypeptides associated with lung/respiratory disorders (especially) and malignancies, such as stimulating and activating peptide factors and transmitters, transcription factors, immunoglobulins and antibodies, antibody receptors, cytokines and chemokines, endogenously produced specific and non-specific enzymes, binding proteins, adhesion molecules and their receptors, cytokine and chemokine receptors, adenosine receptors, bradykinin receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, defensins, growth factors, vasoactive peptides and receptors, binding proteins and malignancy associated proteins (specific target polypeptides given in the specification or the TECHNOLOGY FOCUS section of abstract). The oligos may be used in this way to treat disorders including respiratory obstruction (especially pulmonary obstruction and/or bronchoconstriction) and/or lung inflammation, **allergy**(ies) and/or surfactant hypoproduction which are associated with a disease or condition selected from pulmonary vasoconstriction, inflammation, allergies, **asthma**, impeded respiration, respiratory distress syndrome (RDS), pain, cystic fibrosis (CF), allergic rhynitis (AR), pulmonary hypertension, emphysema, chronic obstructive pulmonary disease (COPD), pulmonary transplantation rejection, pulmonary infections, bronchitis, and/or cancer (claimed).

ADVANTAGE - The oligo(s) are free of adenosine (A), or have a low A content, this minimizes triggering of adenosine receptors during metabolism. The oligo(s) may be administered in combination with other therapeutic agents.

Two hyper sensitive monkeys (ascaris sensitive) were challenged with inhaled adenosine with and without pretreatment with an antisense oligo

(comprising GATGGAGGGCGGCATGGCGGG). The PC40 adenosine was calculated from the data as being equivalent to the amount of adenosine in mg that causes a 40% decrease in dynamic compliance in hyper-sensitive airways. The oligo was administered at 10 mg/day for 2 days by inhalation. On the third day, the PC40 adenosine was measured again. The PC40 value prior to the treatment with the oligo was compared to the PC40 adenosine taken after administration of the oligo. The results indicated showed that any sensitivity to adenosine was completely eliminated by administration of the oligo.
Dwg.0/0

L19 ANSWER 10 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2000-572150 [53] WPIDS
DNC C2000-170608
TI Determining the existence of a correlation between the pathology of a disease and a gene or mRNA encoding a target polypeptide suspected of being associated with the disease.
DC B04 D16
IN NYCE, J W
PA (EPIG-N) EPIGENESIS PHARM INC
CYC 88
PI WO 2000051621 A1 20000908 (200053)* EN 53p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 2000035123 A 20000921 (200065)
BR 2000009247 A 20011120 (200202)
EP 1165093 A1 20020102 (200209) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CN 1348376 A 20020508 (200253)
JP 2002537792 W 20021112 (200275) 104p
KR 2002068262 A 20020827 (200309)
ADT WO 2000051621 A1 WO 2000-US5643 20000302; AU 2000035123 A AU 2000-35123 20000302; BR 2000009247 A BR 2000-9247 20000302, WO 2000-US5643 20000302; EP 1165093 A1 EP 2000-913730 20000302, WO 2000-US5643 20000302; CN 1348376 A CN 2000-806759 20000302; JP 2002537792 W JP 2000-602288 20000302, WO 2000-US5643 20000302; KR 2002068262 A KR 2001-711238 20010903
FDT AU 2000035123 A Based on WO 2000051621; BR 2000009247 A Based on WO 2000051621; EP 1165093 A1 Based on WO 2000051621; JP 2002537792 W Based on WO 2000051621
PRAI US 1999-122950P 19990305
AB WO 200051621 A UPAB: 20001023
NOVELTY - A method for determining the existence of a correlation between the pathology of a disease or condition and a gene or mRNA encoding a target polypeptide suspected of being associated with a disease or condition, is new.

DETAILED DESCRIPTION - A method of determining the existence of a correlation between the function of a disease or condition and a gene or mRNA encoding a target polypeptide suspected of being associated with a disease or condition. The method comprises:

(1) obtaining oligonucleotides (oligos) consisting of up to about 15% adenosine (A) and which is anti-sense to a target selected from target genes and their corresponding mRNAs, genomic and mRNA flanking regions selected from 3' and 5' intron-exon borders and the juxta-section between coding and non-coding regions and all mRNA segments encoding polypeptides associated with a pre-selected disease or condition;

(2) selecting an oligo that significantly inhibits or ablates expression of the polypeptide encoded by the mRNA on in vitro hybridization to the target mRNA;

(3) administering the selected oligo to a subject for in vivo

hybridization to the target mRNA; and

(4) and assessing the subject's function that is associated with the disease or condition before and after administration of the oligo (a change in the function's value greater than about 70% indicates a positive correlation, about 40-70% a possible correlation and below about 30% a lack of correlation).

USE - The anti-sense oligo is administered to the lung, brain, heart, kidney, tumor, blood, skin, eye, scalp, nose panages, testes, cervix, oral cavity, pharynx, eophagus, small or large intestine, synovial tissue, muscle tissue, ovaries, ear canal or in vitro. The disease or condition afflicts the lung, brain, heart, kidney, tumor, blood, immune system, skin, eye, scalp, nose panages, testes, cervix, oral cavity, pharynx, eophagus, small or large intestine, synovial tissue, muscle tissue, ovaries and ear canal. The disease or condition is particularly one which afflicts the lung (particularly being associated with bronchoconstriction, lung inflammation and/or **allergy**(ies)), afflicts the brain or is associated with brain activity, is associated with immune dysfunction (particularly where the target is selected from immunoglobulins, antibody receptors, cytokines, cytokine receptors, gene(s) and the corresponding mRNA(s) encoding them, the genes and mRNA flanking regions and intron and exon borders), afflicts the cardiovascular system, associated with the gastrointestinal system or is associated with a malignancy or cancer (particularly where the target is selected from immunoglobulins and antibody receptors, gene(s) and mRNA(s) encoding them, genes and mRNAs associated with oncogenes and genomic and mRNA flanking regions and intron and exon borders). The target gene is selected from genes and mRNAs encoding polypeptides selected from transcription factors, stimulating and activating factors, cytokines and their receptors, interleukins, interleukin receptors, chemokines, chemokine receptors, endogenously produced specific and non-specific enzymes, immunoglobulins, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters and their receptors, adhesion molecules, defensines, growth factors, vasoactive peptides and their receptors, peptide receptors and binding proteins and target genes and mRNAs corresponding to oncogenes and their flanking regions and intron and exon borders. The encoded polypeptides are selected from NfkappaB Transcription Factor, Interleukin-8 Receptor (IL-8 R), Interleukin-5 Receptor (IL-5 R), Interleukin-4 Receptor (IL-4 R), Interleukin-3 Receptor (IL-3 R), Interleukin-1beta (IL-1beta), Interleukin-1beta Receptor (IL-1beta R), Eotaxin, Tryptase, Major Basic Protein, beta2-adrenergic Receptor Kinase, Endothelin Receptor A, Endothelin Receptor B, Preproendothelin, Bradykinin B2 Receptor, IgE High Affinity Receptor, Interleukin 1 (IL-1), Interleukin 1 Receptor (IL-1 R), Interleukin 9 (IL-9), Interleukin 9 Receptor (IL-9 R), Interleukin 11 (IL-11), Interleukin 11 Receptor (IL-11 R), Inducible Nitric Oxide Synthase, Cyclooxygenase (COX), Intracellular Adhesion Molecule 1 (ICAM-1) Vascular Cellular Adhesion Molecule (VCAM), Rantes, Endothelial Leukocyte Adhesion Molecule (ELAM-1), Monocyte Activating Factor, Neutrophil Chemotactic Factor, Neutrophil Elastase, Defensin 1, 2 and 3, Muscarinic Acetylcholine Receptors, Platelet Activating Factor, Tumor Necrosis Factor alpha, 5-lipoxygenase, Phosphodiesterase IV), Substance P, Substance P Receptor, Histamine Receptor, Chymase, CCR-1 CC Chemokine Receptor, CCR-2 CC Chemokine Receptor, CCR-3 CC Chemokine Receptor, CCR-4 CC Chemokine Receptor, CCR-5 CC Chemokine Receptor, Prostanoid Receptors, GATA-3 Transcription Factor, Neutrophil Adherence Receptor, MAP Kinase, Interleukin-9 (IL-9), NFAT Transcription Factors, STAT 4, MIP-1alpha, MCP-2, MCP-3, MCP-4, Cyclophillins, Phospholipase A2, Basic Fibroblast Growth Factor, Metalloproteinase, CSBP/p38 MAP Kinase, Tryptose Receptor, PDG2, Interleukin-3 (IL-3), Interleukin-1beta (IL-1beta), Cyclosporin A-Binding Protein, FK5-Binding Protein, alpha4eta1 Selectin, Fibronectin, alpha4beta7 Selectin, Mad CAM-1, LFA-1 (CD11a/CD18), PECAM-1, LFA-1, Selectin, C3bi, PSGL-1, E-Selectin, P-Selectin, CD-34, L-Selectin, p150,95, Mac-1 (CD11b/CD18), Fucosyl transferase, VLA-4, CD-18/CD11a, CD11b/CD18, ICAM2 and ICAM3, C5a, CCR3

(Eotaxin Receptor), CCR1, CCR2, CCR4, CCR5, LTB-4, Ap-1 Transcription Factor, Protein kinase C, Cysteinyl Leukotriene Receptor, Tachychinnen Receptors (tach R), IkappaB Kinase 1 and 2, STAT 6, c-mas and NF-Interleukin-6 (NF-IL-6) and their flanking regions and intron and exon borders.
Dwg.0/4

L19 ANSWER 11 OF 16 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AN 2003-19992 BIOTECHDS
TI Treating non-allergic inflammatory diseases, such as psoriasis, eczema, allergic contact dermatitis, latex dermatitis or inflammatory bowel disease by administering an immunostimulatory nucleic acid; involving vector-mediated gene transfer and expression in host cell for use in gene therapy, recombinant vaccine and nucleic acid vaccine preparation
AU KRIEG A M; BERG D J
PA KRIEG A M; BERG D J
PI US 2003050268 13 Mar 2003
AI US 2002-112653 29 Mar 2002
PRAI US 2002-112653 29 Mar 2002; US 2001-279642 29 Mar 2001
DT Patent
LA English
OS WPI: 2003-521815 [49]
AB DERWENT ABSTRACT:
NOVELTY - Treating non-allergic inflammatory disease comprises administering to a subject having or at risk of developing a non-allergic inflammatory disease an immunostimulatory nucleic acid for prevention or treatment of the disease.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) treating inflammatory bowel disease; (2) a pharmaceutical composition; and (3) augmenting Th-1 like immune activation induced by the immunostimulatory nucleic acid.

BIOTECHNOLOGY - Preferred Method: Treating non-allergic inflammatory disease further comprises administering an anti-inflammatory agent comprising corticosteroids, nonsteroidal anti-inflammatory drugs, vitamin A or D analogs, retinoids, cytokines or cytokine receptors, or their agonists or antagonists, antibodies specific for cytokines or cytokine receptors or immunosuppressive agents. The immunostimulatory nucleic acid reduces or prevents non-allergic inflammation in a tissue of the subject. It induces IL-12, IFN-alpha, IFN-gamma or IL-10. It comprises at least one stabilized internucleotide linkage, which is a **phosphorothioate** linkage. It has a backbone completely made up of stabilized internucleotide linkages. It is a **CpG**, T-rich, poly-G or synthetic nucleic acid. It comprises 6-100 or 8-40 bp. The poly-G nucleic acid comprises the formula 5'-X1X2GGGX3X4-3'. X1,X2,X3 or X4 = any nucleotide other than G. The immunostimulatory nucleic acid is administered locally to intact epithelium or systemically. The non-allergic inflammatory disease involves a mucosal epithelium. It comprises psoriasis, eczema, allergic contact dermatitis, latex dermatitis or inflammatory bowel disease. Treating inflammatory bowel disease comprises administering to a subject having or at risk of developing an inflammatory bowel disease the immunostimulatory nucleic acid for prevention or treatment of the disease. The inflammatory bowel disease is ulcerative colitis or Crohn's disease. Augmenting Th-1 like immune activation induced by the immunostimulatory nucleic acid comprises: (1) contacting an immune cell with the immunostimulatory nucleic acid to induce Th-1 like immune activation; and (2) contacting the immune cell with an inhibitor of cyclooxygenase-2 (COX-2) expression. The COX-2 inhibitor is NSAID. The method may also comprise contacting the immune cell with an agent that inhibits PGE2 signaling through its receptor. Preferred Composition: The pharmaceutical composition comprises: (1) the immunostimulatory nucleic acid; (2) a non-allergic inflammatory disease medicament; and (3) a carrier. The carrier is a lotion, cream, ointment or gel.

ACTIVITY - Antiinflammatory; Dermatological; Antipsoriatic; Antiulcer. No biological data given.

MECHANISM OF ACTION - Gene therapy; Vaccine.

USE - The method is useful for treating non-allergic inflammatory diseases, such as psoriasis, eczema, allergic contact dermatitis, latex dermatitis or inflammatory bowel disease e.g., ulcerative colitis or Crohn's disease (claimed).

ADMINISTRATION - Dosage comprises 0.1 microg to 10000 mg, preferably 10 microg to 8000 mg per kg body weight. The pharmaceutical composition is administered via oral, topical, parenteral or transdermal route (claimed). (240 pages)

L19 ANSWER 12 OF 16 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AN 2003-12819 BIOTECHDS
TI Treatment of a subject having, or at risk of developing cancer, involves the use of an immunostimulatory nucleic acid having a modified backbone in combination with a cancer medicament;
phosphorothioate-modified backbone poly-G nucleic acid transfer and expression in host cell for immunostimulant and gene therapy
AU BRATZLER R L; PETERSEN D M
PA BRATZLER R L; PETERSEN D M
PI US 2002156033 24 Oct 2002
AI US 2001-800266 5 Mar 2001
PRAI US 2001-800266 5 Mar 2001; US 2000-187214 3 Mar 2000
DT Patent
LA English
OS WPI: 2003-275279 [27]
AB DERWENT ABSTRACT:
NOVELTY - Treatment (T1) of a subject having cancer involves administering an immunostimulatory nucleic acid (1) having modified backbone and a cancer medicament (M1) selected from chemotherapeutic agent, immunotherapeutic agent, cancer vaccine or hormone therapy. The poly-G nucleic acid is not conjugated to (M1) and is free of **CpG** and T-rich motif.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) Treatment (T3) of a subject having or at risk of developing cancer involving administering an immunostimulatory nucleic acid selected from **CpG** nucleic acid or a non-**CpG** nucleic acid (where the nucleic acid has a **phosphorothioate** modified backbone) and a cancer medicament such as hormone therapy (HT); and (2) A device for delivering immunostimulatory nucleic acid to a subject receiving an intravenous injection, comprising an intravenous device (D1) selected from a bag or a tube and the nucleic acid, where the nucleic acid is coated on an internal surface of (D1) or is embedded within (D1).

ACTIVITY - Cytostatic; Fungicide; Antibacterial; Antiparasitic; Virucide; Antiallergic; Antianemic; Hemostatic.

MECHANISM OF ACTION - Cell growth inhibitor.

USE - The composition is for the treatment of cancer (e.g. bone cancer, brain and CNS cancer, connective tissue cancer, esophageal cancer, eye cancer, Hodgkin's lymphoma, larynx cancer, oral cavity cancer, skin cancer, and testicular cancer), and for preventing allergic responses in those receiving blood transfusions (all claimed). It is also useful for the treatment of fungal, bacterial, parasitic and viral infections.

ADMINISTRATION - Administration is oral, parenteral (including intramuscular or intravenous), intranasal, intratracheal, through inhalation, ocular, vaginal, buccal or rectal. No dosage given.

ADVANTAGE - The combination of the immunostimulatory nucleic acids and the cancer medicament is synergistic. The combination allows for the administration of higher doses of cancer medicaments without as many side effects, and allows for the administration of lower, sub-therapeutic doses of either compound, but with higher efficacy than would otherwise be achieved using such low doses. The immunostimulatory nucleic acids

function by enhancement of anti-body dependent cell cytotoxicity. This mechanism provides long lasting effects of nucleic acids, thus reducing dosing regimens, improving compliance and maintenance therapy, reducing emergency situations and improving quality of life. (32 pages)

L19 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:570637 CAPLUS
DN 139:132442
TI Methods and products for enhancing immune responses using imidazoquinoline compounds in combination with modified immunostimulatory oligonucleotide
IN Krieg, Arthur M.; Schetter, Christian; Bratzler, Robert L.; Vollmer, Jorg; Jurk, Marion; Bauer, Stefan
PA University of Iowa Research Foundation, USA
SO U.S. Pat. Appl. Publ., 112 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003139364	A1	20030724	US 2002-272502	20021015
US 2001-329208P	P	20011012		

AB The invention involves administration of an imidazoquinoline agent in combination with another therapeutic agent. The combination of drugs may be administered in synergistic amts. or in various dosages or at various time schedules. The invention also relates to kits and compns. concerning the combination of drugs. The combinations can be used to enhance ADCC, stimulate immune responses and/or patient and treat certain disorders. Specifically, the imidazoquinoline compns. R-848 is used which is shown to be more potent inducer of proinflammatory cytokines NF-.kappa.B in 293T cells by reconstitution of TLR9 signaling through co-transfecting TLR9, TLR8 and TLR7 into 293T cell. Furthermore, **CpG** oligonucleotides (ODNs, in particular, **CpG** ODN #7909) and R-848 are tested either together or individually for their ability to augment a cytolytic T lymphocyte response against antigen (e.g., HBsAg) in vivo using mouse model. The combination of R-848 and **CpG** ODN together is shown to result in an additive effect; while no augmentation of the CTL response over antigen alone is obsd. using control ODN either alone or with R-848. The distribution of antibody isotype also shows **CpG** ODN produces higher levels of IgG2a antibodies regardless of whether R-848 is present, and R-848 appears to increase the level of IgG2a and decrease the level of IgG1 as compared to the antigen alone response.

L19 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:154198 CAPLUS
DN 138:203655
TI Oligonucleotides containing stimulatory **phosphorothioate** motif and neutralizing motif for treating infections, allergies and cancers
IN Krieg, Arthur M.; Vollmer, Jorg; Ulhman, Eugen
PA Coley Pharmaceutical Group, Inc., USA; Coley Pharmaceutical G.m.b.H.; University of Iowa Research Foundation
SO PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003015711	A2	20030227	WO 2002-US26468	20020819
WO 2003015711	C2	20030410		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	US 2003148976	A1	20030807	US 2002-224523	20020819
PRAI	US 2001-313273P	P	20010817		
	US 2002-393952P	P	20020703		

AB A class of immunostimulatory nucleic acids having at least two functionally and structurally defined domains is provided. The nucleic acids or oligodeoxynucleotides contg. a combination of a stimulating motif (i.e. **CpG**) and a neutralizing motif (i.e. CG-rich palindrome or CG repeats) are, surprisingly, highly immunostimulatory. This class of combination motif immunostimulatory nucleic acids characteristically activate B cells and NK cells, and also induce prodn. of type I interferon. The immunostimulatory nucleic acids or oligonucleotides are therefore, useful for treating a variety of immune related disorders such as cancer, infectious disease, and allergic disorders.

L19 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:736889 CAPLUS
DN 137:273194
TI Modulation of immunostimulatory activity of immunostimulatory oligonucleotide analogs by positional chemical changes
IN Kandimalla, Ekambar R.; Zhao, Qiuyan; Yu, Dong; Agrawal, Sudhir
PA USA
SO U.S. Pat. Appl. Publ., 41 pp., Cont.-in-part of U.S. Ser. No. 712,898.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002137714	A1	20020926	US 2001-965116	20010926
PRAI	US 2000-235452P	P	20000926		
	US 2000-235453P	P	20000926		
	US 2000-712898	A2	20001115		

OS MARPAT 137:273194
AB The invention relates to the therapeutic use of oligonucleotides or oligonucleotide analogs as immunostimulatory agents in immunotherapy applications. The invention provides methods for enhancing the immune response caused by immunostimulatory oligonucleotide compds. A study of the structure-activity relationships of modified **CpG** oligodeoxynucleotide phosphorothioates was made.

L19 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:463662 CAPLUS
DN 137:293467
TI **Phosphorothioate** oligonucleotides: looking for the motif(s) possessing immunostimulatory activities in humans
AU Brugnolo, Francesca; Annunziato, Francesco; Sampognaro, Salvatore; Manuelli, Cinzia; Cosmi, Lorenzo; Romagnani, Sergio; Maggi, Enrico; Parronchi, Paola
CS Department of Internal Medicine, University of Florence, Florence, Italy
SO Advances in Experimental Medicine and Biology (2001), 495(Progress in Basic and Clinical Immunology), 261-264
CODEN: AEMBAP; ISSN: 0065-2598
PB Kluwer Academic/Plenum Publishers
DT Journal
LA English
AB **Phosphorothioate** oligonucleotides (PS-ODNs) showed various effects on human cells, inducing B cell proliferation and prodn. of cytokines from cells of innate immunity. PS-ODNs also shifted the

functional profile of allergen-specific T cells from a prevalent Th2 towards a prevalent Th1-like phenotype. These effects were independent of the absence or presence of classic **CpG** motifs, indicating that immunostimulatory sequences active in humans are different from those described in mice. PS-ODNs in which **CpG** dinucleotides were inverted into GpC still retained a significant effect on B and T cells.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 07:59:41 ON 17 SEP 2003)

FILE 'BIOSIS, MEDLINE, AGRICOLA, EMBASE, CABA, WPIDS, JAPIO, BIOTECHDS, LIFESCI, CAPLUS' ENTERED AT 08:01:24 ON 17 SEP 2003

```
                E BRATZLER ROBERT L/AU
L1             41 S E1-E3
                E PETERSEN DEANNA M/AU
L2              7 S E3
                E FOURON YVES/AU
L3             31 S E1-E3
L4             73 S L1-L3
L5              5 S L4 AND (ASTHMA OR ALLERGIC OR ALLERGY)
L6              4 S L5 AND CPG
L7             27 S L4 AND (CPG OR IMMUNOSTIMULATORY OR NUCLEIC ACID)
L8             11 DUP REM L7 (16 DUPLICATES REMOVED)
L9         418622 S ASTHMA OR ALLERGY
L10         29905 S CPG OR NUCLEIC ACID (5A) ADJUVANT
L11          1292 S L9 AND (REFRACTORY OR HYPORESPONSIVE OR HYPO-RESPONSIVE OR N
L12           785 DUP REM L11 (507 DUPLICATES REMOVED)
L13           523 S L9 AND L10
L14           285 DUP REM L13 (238 DUPLICATES REMOVED)
L15             1 S L12 AND L14
L16           285 S L13 AND L14
L17           161 S L16 AND ASTHMA
L18           163 S L16 AND ALLERGY
L19            16 S L18 AND PHOSPHOROTHIOATE

=> s l17 and phosphorotioate
L20             0 L17 AND PHOSPHOROTIOATE

=> s l17 and modified backbone
L21             1 L17 AND MODIFIED BACKBONE

=> d bib ab

L21  ANSWER 1 OF 1  WPIDS  COPYRIGHT 2003 THOMSON DERWENT on STN
AN   2002-723213 [78]   WPIDS
DNC  C2002-204705
TI   New compositions comprising CpG-like immunostimulatory nucleic
     acids, useful for treating or preventing infectious diseases, cancer,
     allergy, asthma, immunodeficiency, anemia,
     thrombocytopenia or neutropenia.
DC   B04 C06 D16
IN   SCHETTER, C; VOLLMER, J
PA   (COLE-N) COLEY PHARM GROUP LTD
CYC  100
PI   WO 2002069369 A2 20020906 (200278)* EN  148p
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
            NL OA PT SD SE SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
            KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
```

RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

ADT WO 2002069369 A2 WO 2001-IB2888 20011210

PRAI US 2000-254341P 20001208

AB WO 200269369 A UPAB: 20021204

NOVELTY - Compositions, which comprise a pharmaceutical carrier and an immunostimulatory nucleic acid having a sequence including at least the formula (I), (II) or (III), are new.

DETAILED DESCRIPTION - Compositions comprising an immunostimulatory nucleic acid having a sequence, including at least any one of the following formulae, are new.

5' X1X2CGX3X4 3' (I) 5' X1X2ZYX3X4 3' (II) 5' X1X2C1GX3X4 3' (III).

C = methylated;

Y = inosine, 2-aminopurine, xanthosine, N7-methyl-xanthosine, nebularine or dSpacer;

Z = cytosine, 2'-deoxyuridine (dU), 5-fluoro-2'-dU or dSpacer, and where Z is not cytosine when Y is inosine;

C1 = cytosine;

I = inosine; and

X1, X2, X3 and X4 = nucleotides.

An INDEPENDENT CLAIM is also included for a method for inducing an immune response by administering to a subject the novel composition.

ACTIVITY - Antimicrobial; Cytostatic; Antiallergic; Antiasthmatic; Immunostimulant; Antianemic; Hemostatic.

MECHANISM OF ACTION - Interleukin-Inducer-1-Beta; Interleukin-Inducer-2; Interleukin-Inducer-6; Interleukin-Inducer-12; Interleukin-Inducer-18; TNF-Inducer-Alpha; Interferon-Inducer-Alpha; Interferon-Inducer-Gamma.

Peripheral blood monocytes (PBMC) (3 multiply 106 cells/ml) obtained from several blood donors were incubated for 8 hours with 6 micro g/ml of the composition containing oligodeoxynucleotide (ODN) 2006, 2117, 2137, or 1 micro g/ml lipopolysaccharide (LPS) as positive control. Negative controls were similarly incubated for 8 hours in the absence of added ODN or LPS. After 8 hours, supernatants were collected and IL-1 beta (which plays a role in the stimulation of B, T and NK cells, and participates in the conversion of Langerhans cells to professional antigen-presenting dendritic cells, and acts as a chemoattractant for leukocytes) was measured by enzyme linked immunosorbent assay (ELISA). Results showed that **CpG** ODN were potent inducers of IL- beta secretion.

USE - The compositions are useful for inducing an immune response in a subject, e.g. dog, cat, horse, cow, pig, sheep, goat, rabbit, guinea pig, non-human primate, chicken or fish. The compositions are useful for treating or preventing infectious diseases, cancer, **allergy** or **asthma**. The compositions are also useful for enhancing or stimulating bone marrow proliferation in a subject who has or is at risk of developing an immunodeficiency, particularly in a subject undergoing chemotherapy. The compositions are also useful for enhancing erythropoiesis in a subject who has or is at risk of developing anemia, for enhancing thrombopoiesis in a subject who has or is at risk of developing thrombocytopenia, for enhancing neutrophil proliferation in a subject who has or is at risk of developing neutropenia, or for inducing cytokine (e.g. interleukin (IL)-1 beta , IL-2, IL-6, IL-12, IL-18, tumor necrosis factor (TNF)- alpha , interferon (IFN)- alpha or IFN- gamma) production. (All claimed).

Dwg.0/18

=>

---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	176.49	177.12

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-5.21	-5.21

STN INTERNATIONAL LOGOFF AT 08:22:09 ON 17 SEP 2003

ZA 2002001959 A 20030528 (200341) 178p

ADT WO 2001022990 A2 WO 2000-US26527 20000927; AU 2000076190 A AU 2000-76190 20000927; EP 1220684 A2 EP 2000-965477 20000927, WO 2000-US26527 20000927; JP 2003510290 W WO 2000-US26527 20000927, JP 2001-526199 20000927; ZA 2002001959 A ZA 2002-1959 20020308

FDT AU 2000076190 A Based on WO 2001022990; EP 1220684 A2 Based on WO 2001022990; JP 2003510290 W Based on WO 2001022990

PRAI US 1999-156147P 19990927

AB WO 200122990 A UPAB: 20010603

NOVELTY - Methods for improving the efficacy (e.g. reducing the dosage required and/or side effects) of treatments involving the administration of interferon (IFN)- alpha , comprising co-administering the IFN- alpha with an isolated **immunostimulatory nucleic acid** (INA), are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a method (I) of administering interferon (IFN)- alpha , comprising administering an isolated **immunostimulatory nucleic acid** (INA);

(2) a method (II) of supplementing IFN- alpha treatment comprising administering to a subject in need of IFN- alpha treatment, IFN- alpha and an isolated INA;

(3) a method (III) of treating a subject to activate interferon-producing cells (IPC) of a subject, comprising:

(a) isolating IPCs from a subject in need of treatment;

(b) culturing the IPCs in vitro;

(c) contacting the IPCs in vitro with an isolated INA; and

(d) returning the contacted IPCs to the subject;

(4) a method (IV) of increasing efficacy of IFN- alpha treatment of a subject, comprising:

(a) administering to a subject a composition comprising IFN- alpha ; and

(b) co-administering to the subject a composition comprising an INA which, together with the IFN- alpha , is an effective IFN- alpha treatment (the efficacy of the IFN- alpha treatment is greater than the efficacy of administering the same amount of IFN- alpha in the absence of the INA);

(5) a method (V) of decreasing a dose of an IFN- alpha effective for treating a subject, comprising:

(a) administering to a subject a composition comprising IFN- alpha ;

(b) co-administering to the subject a composition comprising an INA which, together with the IFN- alpha , is an effective IFN- alpha treatment (the amount of the IFN- alpha administered is less than the amount required in the absence of the INA);

(6) a method (VI) of preventing an IFN- alpha treatment-related side effect in a subject undergoing treatment with IFN- alpha , comprising:

(a) administering to a subject in need of treatment a composition comprising IFN- alpha s; and

(b) co-administering to the subject a composition comprising an INA which together with the IFN- alpha is an effective IFN- alpha treatment (an IFN- alpha related side effect is reduced in comparison to the side effect when IFN- alpha s is administered in the absence of co-administering the INA);

(7) a method (VII) of enhancing efficacy of IFN- alpha treatment in a subject, comprising:

(a) administering to a subject in need of treatment, a composition comprising IFN- alpha for treating a disorder in the subject;

(b) isolating natural interferon-producing cells (IPCs) from a donor;

(c) contacting he isolated IPCs ex vivo with a composition comprising an INA for inducing the IPCs to release IFN- alpha ; and

(d) administering the contacted cells to the subject;

(8) a method (VIII) of supporting survival of natural interferon-producing cells (IPCs) in vitro, comprising:

(a) isolating IPCs from a subject;

(b) culturing the IPCs in a sterile medium suitable for tissue culture; and

(c) contacting the IPCs in vitro with an INA which supports the growth of the IPCs in the absence of interleukin (IL)-3;

(9) a method (IX) of stimulating isolated interferon-producing cells (IPCs) in vitro, comprising:

(a) isolating IPCs from a subject;

(b) culturing the IPCs in a sterile medium suitable for tissue culture; and

(c) contacting the IPCs in vitro with an INA to induce secretion of at least 1 type 1 interferon;

(10) a method (X) of stimulating production of a number of type 1 IFN subtypes, comprising contacting IPCs with an INA to induce secretion of at least 2 type 1 IFNs;

(11) a method (XI) of inhibiting IL-12 production, comprising contacting IL-12 producing cells, in the presence of interferon-producing cells conditions in which the IL-12 producing cells normally produce IL-12, with an INA that induces secretion of type 1 IFN;

(12) an isolated nucleic acid comprising one of 37 defined nucleotide sequences ((N1)-(N37)) given in the specification; and

(13) a composition comprising (XI) and IFN- alpha .

USE - Methods for improving the efficacy (e.g. reducing the dosage required and/or side effect) of treatments involving the administration of interferon (IFN)- alpha to a subject. The subject is suffering from a proliferative disorder (e.g. hairy cell leukemia, chronic myelogenous leukemia, cutaneous T-cell leukemia, multiple myeloma, follicular lymphoma, malignant melanoma, squamous cell carcinoma, AIDS (acquired immunodeficiency syndrome)-related Kaposi's sarcoma, renal cell carcinoma, prostate carcinoma, bladder cell carcinoma, cervical dysplasia and/or colon carcinoma) and/or a viral infection (e.g. hepatitis B, hepatitis C, condyloma acuminatum, human immunodeficiency virus, herpes, cytomegalovirus, Epstein-Barr virus and/or papillomavirus).

ADVANTAGE - The administration of the INA improves the efficacy of the IFN- alpha therapy, e.g. by reducing the side effects associated with IFN- alpha administration.

Dwg.0/18

L8 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 7

AN 1977:202832 BIOSIS

DN BA64:25196

TI **NUCLEIC-ACID** RELATED COMPOUNDS PART 25 SYNTHESES OF ARABINO XYLO AND LYXO ANHYDRO SUGAR NUCLEOSIDES FROM TUBERCIDIN RIBO EPOXIDE.

AU ROBINS M J; **FOURON Y**; MUHS W H

SO CAN J CHEM, (1977) 55 (7), 1260-1267.
CODEN: CJCHAG. ISSN: 0008-4042.

FS BA; OLD

LA Unavailable

AB Treatment of the trans iodohydrin acetate, 4-amino-7-(3-iodo-3-deoxy-2-O-acetyl-5-O-[2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl]-.beta.-D-xylofuranosyl)pyrrolo[2,3-d]pyrimidine with methanolic ammonia gave 2',3'-anhydrotubercidin (3) in 96% yield. N4,N4,O5'-Tribenzoylation of 3 gave 4, which is stabilized against intramolecular cyclization. Treatment of 4 with boron trifluoride etherate (3',5'-benzoxonium ion formation) followed by deblocking gave 4-amino-7-.beta.-D-xylofuranosylpyrrolo[2,3-d]pyrimidine (5) in 91% overall yield from tubercidin. The 3',5'-O-isopropylidene derivative (6a) of 5 was mesylated to give 6b which was deprotected in acid and the resulting trans hydroxy mesylate was treated with base to give 4-amino-7-(2,3-anhydro-.beta.-D-lyxofuranosyl)pyrrolo[2,3-d]pyrimidine. This lyxo epoxide was treated with sodium benzoate to give 4-amino-7-.beta.-D-arabinofuranosylpyrrolo[2,3-d]pyrimidine. Biochemical, spectroscopic and chemical properties of these

semisynthetic antibiotic analogues of biologically active adenine nucleosides are discussed.

L8 ANSWER 10 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 8
AN 1977:159809 BIOSIS
DN BA63:54673
TI **NUCLEIC-ACID** RELATED COMPOUNDS PART 22 TRANSFORMATION OF RIBO NUCLEOSIDE 2 3-O ORTHO ESTERS INTO HALO SUGAR NUCLEOSIDES DEOXY SUGAR NUCLEOSIDES AND EPOXY SUGAR NUCLEOSIDES USING ACYL HALIDES MECHANISM AND STRUCTURE OF PRODUCTS.
AU ROBINS M J; MENGEL R; JONES R A; **FOURON Y**
SO J AM CHEM SOC, (1976) 98 (25), 8204-8213.
CODEN: JACSAT. ISSN: 0002-7863.
FS BA; OLD
LA Unavailable
AB Treatment of 2',3'-O-methoxyethylideneadenosine (2) with pivalic acid chloride in refluxing pyridine gave an unresolved mixture of 6-N-pivalamido-9-(3-chloro-3-deoxy-2-O-acetyl-5-O-pivalyl-.beta.-D-xylofuranosyl)purine (4a) and its 2'-chloroarabino isomer (3a) as the major product. 6-N-pivalamido-9-(3-chloro-3-deoxy-2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-.beta.-D-xylofuranosyl)purine (4b) and its 2'-chloroarabino isomer (3b) were produced by acylation reactions involving a 2',3'-O-ketene acetal (11) which is in equilibrium with the initially formed 2',3'-acetoxonium ion intermediate (10). The structure of the complex 4,4-dimethyl-3-pivaloxypent-2-enoate (DMPP) group was deduced by NMR and mass spectroscopy and verified by synthesis of ethyl DMPP (9) from ethyl orthoacetate and pivalyl chloride/NaI. Treatment of 2 with pivalyl chloride and excess NaI in refluxing pyridine gave the corresponding 3'-iodoxylo and 2'-iodoarabino DMPP-blocked nucleosides (4c and 3c) in good combined yield accompanied by unsaturated products. The absence of the corresponding acetyl iodo derivatives was rationalized on the basis of greater acylating activity of pivalyl iodide (generated in situ) in the postulated mechanistic sequence involving ketene acetal intermediates. A pivalylketene acetal derivative (14) was isolated and converted to 3c and 4c under the reaction conditions. Treatment of 3a,4a with tri-n-butyltin hydride or of 3c and 4c under catalytic hydrogenolysis conditions gave 2'-deoxyadenosine (7) and 3'-deoxyadenosine (cordycepin) (8), respectively, after deblocking. The ribo epoxide, 9-(2,3-anhydro-.beta.-D-ribofuranosyl)adenine (6), was formed on treatment of 3a-c and 4a-c with methanolic sodium methoxide. This proved the 2',3'-trans orientation of halo and acyloxy substituents and provides convenient access to the synthetically useful 6. Spectroscopic identification of products, the acyloxonium ion mediated mechanism and comparison of the route with previously reported procedures are discussed.

L8 ANSWER 11 OF 11 MEDLINE on STN DUPLICATE 9
AN 74174718 MEDLINE
DN 74174718 PubMed ID: 4833508
TI **Nucleic acid** related compounds. 11. Adenosine 2',3'-ribo-epoxide. Synthesis, intramolecular degradation, and transformation into 3'-substituted xylofuranosyl nucleosides and the lyxo-epoxide.
AU Robins M J; **Fouron Y**; Mengel R
SO JOURNAL OF ORGANIC CHEMISTRY, (1974 May 31) 39 (11) 1564-70.
Journal code: 2985193R. ISSN: 0022-3263.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197407
ED Entered STN: 19900310
Last Updated on STN: 19900310

Entered Medline: 19740731

=> s asthma or allergy
L9 418622 ASTHMA OR ALLERGY

=> s cpg or nucleic acid (5a) adjuvant
L10 29905 CPG OR NUCLEIC ACID (5A) ADJUVANT

=> s l9 and (refractory or hyporesponsive or hypo-responsive or non-responsive)
L11 1292 L9 AND (REFRACTORY OR HYPORESPONSIVE OR HYPO-RESPONSIVE OR NON-RESPONSIVE)

=> dup rem l11
PROCESSING IS APPROXIMATELY 85% COMPLETE FOR L11
PROCESSING COMPLETED FOR L11
L12 785 DUP REM L11 (507 DUPLICATES REMOVED)

=> s l9 and l10
L13 523 L9 AND L10

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14 285 DUP REM L13 (238 DUPLICATES REMOVED)

=> s l12 and l14
L15 1 L12 AND L14

=> d bib ab

L15 ANSWER 1 OF 1 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AN 2002-16855 BIOTECHDS
TI Skin-derived macrophages from Leishmania major-susceptible mice exhibit interleukin-12-and interferon-gamma-independent nitric oxide production and parasite killing after treatment with immunostimulatory DNA; useful for infectious disease, tumor, autoimmune disease, **allergy** gene therapy and nucleic acid vaccine
AU VON STEBUT E; BELKAID Y; NGUYEN B; WILSON M; SACKS DL; UDEY MC
CS Univ Mainz; NIAID; NCI
LO von Stebut E, Univ Mainz, Dept Dermatol, Langenbeckstr 1, D-55131 Mainz, Germany
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY; (2002) 119, 3, 621-628 ISSN: 0022-202X
DT Journal
LA English
AB AUTHOR ABSTRACT - Co-administration of **CpG**-containing immunostimulatory oligodeoxynucleotidesand parasite antigen protects susceptible BALB/c mice from otherwise progressive infection with Leishmania major. Although the protective effect of **CpG** -containing immunostimulatory oligodeoxynucleotides is clearly dependenton endogenous interleukin-12 and interferon-gamma production, the source ofthese Th1-promoting cytokines in infected mice is unknown. In contrast tomacrophages from Leishmania-resistant C57BL/6 mice, macrophages from susceptible BALB/c mice are **hyporesponsive** to stimulation with lipopolysaccharideand interferon-gamma. While studying interactions of various antigen-presenting cells with Leishmania, we found that BALB/c inflammatory skin macrophages, whether Leishmania-infected or uninfected, produced large amounts ofinterleukin-12 when treated with **CpG**-containing immunostimulatory oligodeoxynucleotides. Like lipopolysaccharide, **CpG**-containing immunostimulatory oligodeoxynucleotides induced production of interferon-gamma and release of nitric oxide by skin macrophages. Studies using skin macrophages from interleukin-12- and

interferon-gamma-deficient BALB/c mice demonstrated that nitric oxide release was not dependent on interleukin-12 and interferon-gamma production. Approximately 44% and 27% of intracellular Leishmania major amastigotes were killed by infected skin macrophages within 72 h upon stimulation with **CpG**-containing immunostimulatory oligodeoxynucleotides and lipopolysaccharide, respectively. Parasite killing by macrophages was independent ofendogenous interferon-gamma production, but was strongly enhanced by exogenous interferon-gamma. Parasite elimination was dependent on the inductionof nitric oxide, however. In vivo, injection of **CpG**-containing immunostimulatory oligodeoxynucleotides into lesional skin reduced the parasite burdenapproximate to50-fold within the first 5 d of infection prior to full generation of a Th response. These results suggest that skin macrophages, constituting the principal reservoir of parasites in infected susceptible mice, produce Th1-promoting cytokines in response to **CpG**-containing immunostimulatory oligodeoxynucleotides. In addition, **CpG**-containing immunostimulatory oligodeoxynucleotides may also act locally on skin macrophages to facilitateLeishmania clearance by inducing nitric oxide production. (8 pages)

```
=> s l13 and l14
L16         285 L13 AND L14

=> s l16 and asthma
L17         161 L16 AND ASTHMA

=> s l16 and allergy
L18         163 L16 AND ALLERGY

=> s l18 and phosphorothioate
L19          16 L18 AND PHOSPHOROTHIOATE

=> d bib ab 1-16

L19  ANSWER 1 OF 16  BIOSIS  COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN   1999:355473  BIOSIS
DN   PREV199900355473
TI   Oligodeoxynucleotides containing CpG motifs induce IL-12, IL-18
     and IFN-gamma production in cells from allergic individuals and inhibit
     IgE synthesis in vitro.
AU   Bohle, Barbara; Jahn-Schmid, Beatrice; Maurer, Dieter; Kraft, Dietrich;
     Ebner, Christof (1)
CS   (1) Department of General and Experimental Pathology, University of
     Vienna, Waehringer Guertel 18-20, A-1090, Vienna Austria
SO   European Journal of Immunology, (July, 1999) Vol. 29, No. 7, pp.
     2344-2353.
     ISSN: 0014-2980.
DT   Article
LA   English
SL   English
AB   The effects of phosphorothioate oligonucleotides containing
     CpG motifs (CpG-ODN) on cultured cells from allergic
     patients and non-atopic individuals were investigated. In peripheral blood
     mononuclear cells (PBMC) CpG-ODN led to a significant increase
     of IFN-gamma. By intracellular cytokine staining, IFN-gamma production
     could be attributed to NK cells and inhibition experiments indicated an
     IL-12-dependent mechanism. Moreover, CpG-ODN increased mRNA
     expression of IL-12 and IL-18 in PBMC. In this respect, no significant
     difference between allergic and non-atopic individuals was observed.
     Monocyte-derived dendritic cells were identified as one IL-12- and
     IL-18-producing source. In addition, stimulation of PBMC derived from
```

atopic patients with **CpG**-ODN led to a considerable increase of polyclonal IgG and IgM synthesis. In contrast, the production of total IgE was suppressed. **CpG**-ODN induced a significant rise of IgG and IgM specific for allergens to which the patients were sensitized, whereas allergen-specific IgE levels remained unchanged. Our data suggest that **CpG**-ODN display a strong influence on the ongoing immune response and might represent potential adjuvants for specific immunotherapy of type I **allergy**.

L19 ANSWER 2 OF 16 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 2001331889 EMBASE
TI Immunostimulatory DNA inhibits IL-4-dependent IgE synthesis by human B cells.
AU Horner A.A.; Widhopf G.F.; Burger J.A.; Takabayashi K.; Cinman N.; Ronaghy A.; Spiegelberg H.L.; Raz E.
CS Dr. A.A. Horner, University of California, 9500 Gilman Dr., San Diego, CA 92093-0663, United States
SO Journal of Allergy and Clinical Immunology, (2001) 108/3 (417-423).
Refs: 36
ISSN: 0091-6749 CODEN: JACIBY
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB Background: Immunostimulatory sequence oligodeoxynucleotide (ISS-ODN) is a potent antiallergic immunomodulating agent in mice. However, few studies have addressed its antiallergic potential in human subjects. Objective: We sought to determine whether a **phosphorothioate** ISS-ODN could inhibit IL-4-dependent IgE synthesis by human B cells. Methods: Initially, nonatopic- and atopic-donor PBMCs were incubated with ISS-ODN or mutated oligodeoxynucleotide, and cytokine production and B-cell expression of IFN-.gamma. receptor and IL-4 receptor were measured by using ELISA and flow cytometry, respectively. In subsequent studies atopic-donor PBMCs were incubated with IL-4 alone or with ISS-ODN or mutated oligodeoxynucleotide. After 14 days, IgE production and IgM, IgG, and IgA production were determined by using ELISA. In select IgE studies cytokines were neutralized with mAbs. Results: ISS-ODN induced IL-12, IFN-.alpha. IFN-.gamma., IL-10, and IL-6 production from both nonatopic- and atopic-donor PBMCs. ISS-ODN also increased IFN-.gamma. receptor and inhibited IL-4 receptor expression on B cells from both donor populations. Furthermore, ISS-ODN inhibited IL-4-dependent IgE production by atopic-donor PBMCs. Neutralization of IL-12, IFN-.alpha., IFN-.gamma., and IL-10, but not IL-6, attenuated the inhibitory activity of ISS-ODN on IgE production. In contrast to its inhibition of IgE synthesis, ISS-ODN stimulated the production of IgM, IgG, and IgA. Conclusion: These in vitro studies demonstrate that **phosphorothioate** ISS-ODN elicits an innate immune response by PBMCs, which inhibits IL-4-dependent IgE synthesis. In addition, these results provide further support for consideration of ISS-ODN therapy for the treatment of allergic disease in clinical practice.

L19 ANSWER 3 OF 16 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 1999408447 EMBASE
TI **Phosphorothioate** oligodeoxynucleotides promote the in vitro development of human allergen-specific CD4+ T cells into Th1 effectors.
AU Parronchi P.; Brugnolo F.; Annunziato F.; Manuelli C.; Sampognaro S.; Mavilia C.; Romagnani S.; Maggi E.
CS Dr. S. Romagnani, Dipartimento di Medicina Interna, Sezione di Immunoallergologia, Policlinico di Careggi, Viale Morgagni 85, 50134 Florence, Italy. s.romagnani@mednuc2.dfc.unifi.it
SO Journal of Immunology, (1 Dec 1999) 163/11 (5946-5953).
Refs: 41

ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB DNA vaccination is an effective approach in inducing the switch of murine immune responses from a Th2 to a Th1 profile of cytokine production that has been related to the activity of unmethylated **CpG** motifs present in bacterial, but not mammalian, DNA. We report here that some synthetic **phosphorothioate**, but not phosphodiester, oligodeoxynucleotides (ODNs) were able to induce B cell proliferation and to shift the in vitro differentiation of Dermatophagoides pteronyssinus group 1-specific human CD4+ T cells from atopic donors into Th cell effectors showing a prevalent Th1, instead of Th2, cytokine profile. This latter effect was completely blocked by the neutralization of IL-12 and IFN (.alpha. and .gamma.) in bulk culture, suggesting that the Th1-inducing activity of **phosphorothioate** ODNs was mediated by their ability to stimulate the production of these cytokines by monocytes, dendritic, and NK cells. Cytosine methylation abolished the Th1-inducing activity of ODNs; however, **CpG** dinucleotide-containing ODNs exhibited the Th1-shifting effect independently of the presence or the absence of **CpG** motifs (5'-pur-pur-**CpG**-pyr-pyr-3'). Moreover, the inversion of **CpG** to GpC resulted only in a partial reduction of this activity, suggesting that the motif responsible for the Th1-skewing effect in humans is at least partially different from that previously defined in mice. These results support the concept that the injection of allergens mixed to, or conjugated with, appropriate ODNs may provide a novel allergen-specific immunotherapeutic regimen for the treatment of allergic disorders.

L19 ANSWER 4 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2003-493178 [46] WPIDS
DNC C2003-131980
TI Immunostimulatory oligonucleotides for use in treating cancer, skin disorders, **asthma**, **allergy**, comprises two oligonucleotides linked at their 3' ends, a nucleobase or sugar by a non-nucleotidic linker.
DC B04 D16
IN AGRAWAL, S; BHAGAT, L; KANDIMALLA, E R; YU, D
PA (HYBR-N) HYBRIDON INC
CYC 89
PI WO 2003035836 A2 20030501 (200346)* EN 96p
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
ADT WO 2003035836 A2 WO 2002-US33756 20021022
PRAI US 2001-344767P 20011024
AB WO2003035836 A UPAB: 20030719
NOVELTY - An immunomer comprising at least two oligonucleotides linked at their 3' ends, or internucleoside linkages or a functionalized nucleobase or sugar by a non-nucleotidic linker, where at least one of the oligonucleotides is an immunostimulatory oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) an immunomer conjugate comprising the above immunomer, and an antigen conjugated to the immunomer at a position other than the accessible 5' end; and

(2) a pharmaceutical formulation comprising the above immunomer.

ACTIVITY - Cytostatic; Immunosuppressive; Antibacterial; Virucide; Antiparasitic; Antiinflammatory; Antiallergic; Antiasthmatic; Dermatological.

No biological data given.

MECHANISM OF ACTION - Vaccine; Stimulator of immune response.

To test the effect on immunostimulatory activity of **CpG** DNA containing branched alkyl-linkers, two branched alkyl-linkers containing a hydroxyl or an amine functional group were incorporated into parent **CpG** DNA (CTATCTGACGTTCTCTGT) and the effects on immunostimulatory activity of the resulting modified **CpG** DNAs (CTATCTGCGTTCTCTGT, CTATCTACGTTCTCTGT, CTACTGACGTTCTCTGT) were examined. The data obtained with modified **CpG** DNAs containing aminolinkers at different nucleotide positions, in BALB/c mouse spleen cell cultures (proliferation) and in vivo (splenomegaly) showed that the **CpG** DNA containing an aminobutyryl propanediol-linker induced spleen cell proliferation in BALB/c mice spleen cell cultures and splenomegaly in BALB/c mice. Parent **CpG** DNA showed a proliferation index of 3.7 plus or minus 0.8 at a concentration of 0.1 micro g/ml. At the same concentration, modified **CpG** DNAs containing amino-linker at different positions caused higher spleen cell proliferation than did the parent **CpG** DNA. As observed with other linkers, when the substitution was placed adjacent to **CpG** dinucleotide, a lower proliferation index was noted compared with parent **CpG** DNA, further confirming that the placement of a linker substitution adjacent to **CpG** dinucleotide had a detrimental effect on immunostimulatory activity. In general, substitution of an amino-linker for 2'-deoxyribonucleoside in the 5'-flanking sequence resulted in higher spleen cell proliferation than found with the substitution in the 3' flanking sequence. Similar results were observed in the splenomegaly assay, confirming the results observed in spleen cell cultures. Modified **CpG** DNAs containing glycerol-linker showed immunostimulatory activity similar to or slightly higher than that observed with modified **CpG** DNA containing an amino-linker.

USE - The immunomer and the immunomer conjugate are useful for generating an immune response in a vertebrate and also for treating a patient having a disease or disorder, such as cancer, autoimmune disorder, airway inflammation, inflammatory disorders, skin disorders, **allergy**, **asthma** or a disease caused by a pathogen. The method comprises administering a vaccine, where the vaccine and immunomer are linked to an immunogenic protein, and further administering an adjuvant (claimed). The immunomer is useful for treating autoimmune disorders, bacteria, parasitic and viral infections in adult and pediatric human and veterinary applications. The immunomers are also useful as adjuvants in combination with DNA vaccines, antibodies, allergens, chemotherapeutic agents and antisense oligonucleotides.

Dwg.0/21

L19 ANSWER 5 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2002-689667 [74] WPIDS
CR 1996-105847 [11]; 1998-272127 [24]; 2000-086224 [07]; 2001-217934 [22]; 2001-280761 [29]; 2001-380456 [40]; 2003-466135 [44]; 2003-512356 [48]
DNC C2002-194884
TI Activating a dendritic cell for cancer immunotherapy or for treating infectious or **allergy** disease, by contacting a dendritic cell with an isolated nucleic acid containing at least one unmethylated **CpG** dinucleotide.
DC B04 D16
IN HARTMANN, G; KRIEG, A M
PA (IOWA) UNIV IOWA RES FOUND
CYC 1
PI US 6429199 B1 20020806 (200274)* 52p
ADT US 6429199 B1 CIP of US 1994-276358 19940715, CIP of US 1995-386063 19950207, CIP of US 1996-738652 19961030, CIP of US 1997-960774 19971030,

US 1998-191170 19981113
FDT US 6429199 B1 CIP of US 6194388, CIP of US 6207646, CIP of US 6239116
PRAI US 1998-191170 19981113; US 1994-276358 19940715; US 1995-386063 19950207; US 1996-738652 19961030; US 1997-960774 19971030
AB US 6429199 B UPAB: 20030729
NOVELTY - Activating (M) or causing maturation of a dendritic cell, comprising contacting a dendritic cell with an isolated nucleic acid containing at least one unmethylated **CpG** dinucleotide, where the nucleic acid is from 8-80 bases in length in an amount effective to activate or cause maturation of the dendritic cell, where the activation is performed ex vivo, is new.

ACTIVITY - Cytostatic; Antiallergic.

MECHANISM OF ACTION - Activator of dendritic cells (claimed); Inducer of dendritic cell maturation.

Mature human dendritic cell (DC) expressed the specific DC marker CD83, while immature DC do not. Mature DC effectively presented antigen and maintained their stimulatory capacity while migrating from peripheral tissues to lymph nodes. Maturation of DC was thought to be essential if these cells were intended to be used for therapeutic strategies where they would be activated ex vivo, pulsed with antigens, and then reinfused into a patient. Freshly isolated DC were incubated for 3 days with granulocyte macrophage-colony stimulating factor (GM-CSF), lipopolysaccharide (LPS) or oligonucleotides. The results showed that in the absence of either GM-CSF or **CpG**, or with the methylated control oligonucleotide 2117: 5'-TQGTQGTTTTGTQGTTTTGTQGTT-3' (2 micro g/ml), survival of cells was poor. The remaining viable cells did not express CD83. Cells incubated with GM-CSF showed low expression of CD86, and only 4.1 % of the cells expressed CD83. If LPS was present in addition to GM-CSF, the percentage of CD83 positive cells was increased to 8.6 %. In contrast, the single addition of the **CpG** oligonucleotide 2006: 5'-TCGTCGTTTTGTCGTTTTGTCGTT-3' rendered 16 % of the DC CD83 positive. The combination of GM-CSF and 2006 enhanced CD83 expression synergistically (37 %). This induction of CD83 expression was **CpG** specific as showed by the control oligonucleotide 2117 in combination with GM-CSF (9.7 %).

USE - (M) is useful for cancer immunotherapy or for treating an infectious disease or **allergy**, by administering an activated dendritic cell that express a specific cancer, microbial or **allergy** causing antigen, to a subject having a cancer including the cancer antigen, to a subject having an infection with a microorganism including the microbial antigen or to a subject having an allergic reaction to the **allergy** causing antigen, where the activated dendritic cell is prepared by (M). (M) is useful for generating a high yield of dendritic cells by administering an isolated nucleic acid containing at least one unmethylated **CpG** dinucleotide, where the nucleic acid is 8-80 bases in length in an amount effective to activate the dendritic cells to a subject, and isolating dendritic cells from the subject. (All claimed).

ADVANTAGE - The use of **CpG** allows the generation of mature dendritic cells from peripheral blood within two days in a well defined system. The application of **CpG** for this purpose is superior to granulocyte macrophage-colony stimulating factor (GM-CSF), which is currently used for this purpose. **CpG** oligonucleotides have a longer half life, are less expensive, and show a greater magnitude of immune effects.

Dwg.2/12

L19 ANSWER 6 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2002-527359 [56] WPIDS
DNC C2002-149289
TI Method for modulating the immunostimulatory effect of an immunostimulatory oligonucleotide compound, and new immunostimulatory oligonucleotide compounds.

DC B02 D16
IN AGRAWAL, S; KANDIMALLA, E R; YU, D; ZHAO, Q
PA (HYBR-N) HYBRIDON INC; (AGRA-I) AGRAWAL S; (KAND-I) KANDIMALLA E R; (YUDD-I) YU D; (ZHAO-I) ZHAO Q
CYC 96
PI WO 2002026757 A2 20020404 (200256)* EN 94p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001094750 A 20020408 (200256)
US 2002137714 A1 20020926 (200265)
EP 1322656 A2 20030702 (200344) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002026757 A2 WO 2001-US30137 20010926; AU 2001094750 A AU 2001-94750 20010926; US 2002137714 A1 Provisional US 2000-235452P 20000926, Provisional US 2000-235453P 20000926, CIP of US 2000-712898 20001115, US 2001-965116 20010926; EP 1322656 A2 EP 2001-975423 20010926, WO 2001-US30137 20010926
FDT AU 2001094750 A Based on WO 2002026757; EP 1322656 A2 Based on WO 2002026757
PRAI US 2000-712898 20001115; US 2000-235452P 20000926; US 2000-235453P 20000926; US 2001-965116 20010926
AB WO 200226757 A UPAB: 20020903
NOVELTY - Positional chemical modifications introduced in immunostimulatory oligonucleotide compounds affect their immunostimulatory capabilities. New imunostimulatory oligonucleotide compounds are claimed.

DETAILED DESCRIPTION - A method for modulating the immunostimulatory effect of an immunostimulatory oligonucleotide compound comprises:

(a) introducing into the immunostimulatory domain a dinucleotide analog that includes a non-naturally occurring pyrimidine base;

(b) introducing into the immunostimulatory domain and/or potentiation domain an immunostimulatory moiety; or

(c) introducing into the oligonucleotide a 3'-3' linkage.

INDEPENDENT CLAIMS are included for the following:

(1) new immunostimulatory oligonucleotide compounds comprising:

(a) an immunostimulatory dinucleotide of formula 5'-pyrimidine purine-3', where pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural or non-natural purine nucleoside;

(b) an immunostimulatory dinucleotide of formula C asterisk pG;

(c) immunostimulatory domains of formula 5'------X1-X2-Y-Z X3-X4------3' (II);

(d) a sequence of formula 5'-Um..U1-X1-X2-Y-Z-X3-X4D1.m 3' (III) and

(2) a method of generating an immune response comprising administering an oligonucleotide analog described in (1).

C asterisk = a cytidine analog;

G = guanosine, 2'-deoxyguanosine or a guanosine analog;

p = an internucleotide linkage selected from phosphodiester, **phosphorothioate** and phosporodithioate;

Y = cytidine, 2'-deoxycytidine, or a non-natural pyrimidine nucleoside;

Z = guanosine, 2'-deoxyguanosine, or a non-natural purine nucleoside;

X1 = a naturally occurring nucleoside or an immunostimulatory moiety selected from a 3C alkyl linker, 2 aminobutyl-1,3-propanediol linker, and beta -L-deoxynucleoside;

X2 = a naturally occurring nucleoside or an immunostimulatory moiety that is an amino linker;

X3 = a naturally occurring nucleoside or an immunostimulatory moiety that is a nucleoside methylphosphonate;

X4 = a naturally occurring nucleoside or an immunostimulatory moiety selected from nucleoside methylphosphonate and 2'-O-methylribonucleoside;
Y = a non-natural pyrimidine nucleoside;
Z = guanosine, 2' deoxy-guanosine or a non-natural purine nucleoside;
X = a naturally occurring nucleoside or an immunostimulatory moiety;
Um-U1 = an upstream potentiation domain where each U is a naturally occurring nucleoside or an immunostimulatory moiety;
D1-Dm = a downstream potentiation domain where each D is a naturally occurring nucleoside or an immunostimulatory moiety; and
m = 0-30.
With the proviso that at least 1 of X1-X4 is an immunostimulatory moiety.
ACTIVITY - Immunostimulatory; Antiviral; Antibacterial; Antiparasitic; Cytostatic; Anitallergic; Antiasthmatic; Respiratory.
The immunostimulatory activity of end-blocked CpG-PS-oligos was studied in a lymphocyte proliferation assay. Mouse spleen lymphocytes were cultured with CpG-PS-oligos at 0.1, 1 and 10 micro g/ml for 48 hours and cell proliferation was determined by 3H uridine incorporation.
Oligo A induced a dose-dependent effect on cell proliferation (proliferation index (PI) 5.0 plus or minus 0.32 at 10 micro g/ml). Oligo B, which consisted of 2 units of A linked by a 3'-5'-linkage, had PI 5.8 plus or minus 0.28 at the same dose. Oligo C, which consisted of 2 units of A linked by a 5'-5'-linkage, had PI 2.0 plus or minus 0.26, showing a significantly lower immunostimulatory activity than observed for A or B. Oligo D, which consisted of 2 units of A linked by a 3'-3' linkage, had PI 7.2 plus or minus 0.5, showing a greater immunostimulatory activity than observed for A or B.
MECHANISM OF ACTION - None given in the source material.
USE - For treating a disease caused by a pathogen, e.g. a virus, parasite or bacterium; cancer; autoimmune disorders (e.g. autoimmune asthma); or airway inflammation or allergy.
The oligonucleotide may be administered in combination with an antibiotic, antigen, allergen, vaccine, antibody, cytotoxic agent, antisense oligonucleotide, gene therapy vector, DNA vaccine or adjuvant, particularly with a chemotherapeutic compound in the treatment of cancer.
Dwg.0/28

L19 ANSWER 7 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2002-130570 [17] WPIDS
DNC C2002-040090
TI New immunostimulatory compositions comprising RNA/DNA hybrid oligonucleotides, useful for enhancing an immune response or inducing cytokines, particularly for treating diseases, e.g. cancer, **allergy** or HIV infection.
DC B04 D16
IN FLORA, M; KLINMAN, D M; MOND, J J
PA (BIOS-N) BIOSYNEXUS INC
CYC 96
PI WO 2001093902 A2 20011213 (200217)* EN 68p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001075294 A 20011217 (200225)
EP 1292331 A2 20030319 (200322) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2001093902 A2 WO 2001-US18276 20010607; AU 2001075294 A AU 2001-75294 20010607; EP 1292331 A2 EP 2001-941989 20010607, WO 2001-US18276 20010607
FDT AU 2001075294 A Based on WO 2001093902; EP 1292331 A2 Based on WO

2001093902
PRAI US 2000-209797P 20000607
AB WO 200193902 A UPAB: 20020313
NOVELTY - An immunostimulatory composition, which comprises at least one oligonucleotide comprising both an RNA region and a DNA region, is new. At least one terminus of the oligonucleotide comprises RNA.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an adjuvant comprising the immunostimulatory composition;

(2) vaccines (I) comprising:

(a) at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA, where the oligonucleotide is associated with a physiological carrier or delivery system;

(b) at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA, and at least one target antigen;

(3) a method of stimulating innate immunity comprising administering at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA, and where the oligonucleotide is associated with a physiological carrier or delivery system;

(4) a method of stimulating global immunity comprising administering at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA, and where the oligonucleotide is associated with a physiological carrier or delivery system;

(5) methods of stimulating a cellular immune response or a humoral immune response comprising administering the vaccine of (Ib); and

(6) a method of making a vaccine comprising associating:

(a) at least one oligonucleotide comprising both an RNA region and a DNA region, where at least one terminus of the oligonucleotide comprises RNA; and

(b) a physiological carrier or delivery system.

ACTIVITY - Immunostimulant; antiallergic; cytostatic; antimicrobial; immunosuppressive; anti-HIV; protozoacide; virucide; hepatotropic; antiinflammatory; antibacterial.

MECHANISM OF ACTION - Gene therapy; cytokine stimulator; vaccine. The stimulation of cytokines interleukin-6 (IL-6) and interferon gamma (IFN-gamma) in human peripheral lymphocytes cultured from four healthy volunteer subjects, designated S1 through S4, was assayed using standard methods. Oligonucleotides DDD and RDR were added to the media of cultured cells to final concentrations of 0.3, 3, or 30 micro g/ml. 24 hours after oligonucleotide addition, Th1 and Th2-type cytokine levels in the media were determined by enzyme linked immunoabsorbant assay (ELISA). The hybrid DNA/RNA oligonucleotides stimulated the production of cytokines implicated in eliciting both Th1 (IFN- gamma) and Th2 T (IL-6) type responses in human peripheral lymphocytes. At the highest concentrations tested, for example, the hybrid RDR molecule was 3-fold more effective at inducing IFN- gamma and 5-fold more effective at stimulating the release of IL-6.

USE - The composition is useful for enhancing an immune response or inducing cytokines. The compositions comprising the oligonucleotides are useful as vaccine adjuvants and in treating diseases, e.g. pathogenic infection, (non-)malignant tumors (e.g. cancers of the brain, lung, ovary, breast, prostate or colon, or carcinomas and sarcomas), autoimmune disease or **allergy** (e.g. allergic rhinitis, hay fever or food allergies), lyme disease, hepatitis, HIV or malaria. The composition is also useful for treating, preventing or ameliorating the symptoms resulting from exposure to a bio-warfare agent, e.g. Ebola, Anthrax or Listeria.

Dwg.0/0

L19 ANSWER 8 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN

AN 2001-273485 [28] WPIDS
DNC C2001-082927
TI Vaccinating against tumors, infectious diseases, allergies and **asthma** using immunostimulatory Py-rich and TG nucleic acids.
DC B04 D16
IN KRIEG, A M; SCHETTER, C; VOLLMER, J; KRIEG, A
PA (COLE-N) COLEY PHARM GMBH; (IOWA) UNIV IOWA RES FOUND
CYC 88
PI WO 2001022972 A2 20010405 (200128)* EN 336p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
AU 2000076153 A 20010430 (200142)
NO 2002001453 A 20020527 (200247)
EP 1221955 A2 20020717 (200254) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
BR 2000014236 A 20021015 (200276)
HU 2002002639 B 20021228 (200308)
CZ 2002001050 A3 20030115 (200309)
KR 2002068509 A 20020827 (200309)
JP 2003510282 W 20030318 (200321) 423p
SK 2002000396 A3 20030401 (200331)
ZA 2002001963 A 20030528 (200341) 378p
ADT WO 2001022972 A2 WO 2000-US26383 20000925; AU 2000076153 A AU 2000-76153 20000925; NO 2002001453 A WO 2000-US26383 20000925, NO 2002-1453 20020322; EP 1221955 A2 EP 2000-965433 20000925, WO 2000-US26383 20000925; BR 2000014236 A BR 2000-14236 20000925, WO 2000-US26383 20000925; HU 2002002639 B WO 2000-US26383 20000925, HU 2002-2639 20000925; CZ 2002001050 A3 WO 2000-US26383 20000925, CZ 2002-1050 20000925; KR 2002068509 A KR 2002-703845 20020323; JP 2003510282 W WO 2000-US26383 20000925, JP 2001-526182 20000925; SK 2002000396 A3 WO 2000-US26383 20000925, SK 2002-396 20000925; ZA 2002001963 A ZA 2002-1963 20020308
FDT AU 2000076153 A Based on WO 2001022972; EP 1221955 A2 Based on WO 2001022972; BR 2000014236 A Based on WO 2001022972; HU 2002002639 B Based on WO 2001022972; CZ 2002001050 A3 Based on WO 2001022972; JP 2003510282 W Based on WO 2001022972; SK 2002000396 A3 Based on WO 2001022972
PRAI US 2000-227436P 20000823; US 1999-156113P 19990925; US 1999-156135P 19990927
AB WO 200122972 A UPAB: 20010522
NOVELTY - A method (I) of stimulating an immune response, comprising administering an immunostimulatory nucleic acid (INA) (selected from a Py-rich nucleic acid and a TG nucleic acid) to a non-rodent subject in sufficient quantity to stimulate an immune response, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a composition (II) comprising a sustained release device including an INA, which is free of unmethylated **CpG** motifs (and is selected from a T-rich nucleic acid and a TG nucleic acid);

(2) a composition (III) comprising an INA which is free of unmethylated **CpG** motifs (and is selected from a T-rich nucleic acid and a TG nucleic acid) and an antigen;

(3) a composition (IV) comprising an INA which is free of unmethylated **CpG** motifs (and is selected from a T-rich nucleic acid and a TG nucleic acid) and an antimicrobial agent;

(4) a composition (V) comprising an INA and an anti-cancer therapy for treating cancers or to reduce the risk of developing a cancer (the INA is selected from a T-rich nucleic acid and a TG nucleic acid);

(5) a composition (VI) comprising an immunostimulatory nucleic acid and/or an **asthma/allergy** treatment for preventing or

treating an immune response associated with exposure to a mediator of **asthma** or **allergy** (the INA is selected from a T-rich nucleic acid, a TG nucleic acid and/or a C-rich nucleic acid);

(6) a composition (VII) comprising an INA selected from 4661 defined nucleic acid sequences given in the specification;

(7) a composition (VIII) an INA comprising (S5) (in which 1 of the Cs is unmethylated and the INA has less than 100 nucleotides); and

(8) a composition (IX) comprising an INA comprising (S6) (in which 1 of the Cs is unmethylated, the INA has less than 100 nucleotides and a phosphodiester backbone) and a sustained release device.

5'-M1TCGTCGTTM2-3' (S5)

M1 = a nucleic acid with at least 1 nucleotide; and

M2 = a nucleic acid having 0-50 nucleotides.

5'-TCGTCGTT-3' (S6)

ACTIVITY - Cytostatic; virucidal; bactericidal; fungicidal; anti-parasitic; immunostimulatory.

MECHANISM OF ACTION - Vaccine.

USE - The method is used to vaccinate subjects such as humans, dogs, cats, horses, cows, pigs, sheep, goats, chickens, monkeys or fish against tumor antigens, viral antigens (e.g. herpesviridae, retroviridae and/or orthomyxoviridae), bacterial antigens (e.g. toxoplasma, haemophilus, campylobacter, clostridium, Escherichia coli and/or staphylococcus), fungal antigens and/or parasitic antigens. The subject has or is at risk of developing cancer (especially), **asthma**, infectious disease and/or an **allergy** and the method is used for preventing that cancer, **asthma**, disease or **allergy**. The cancer is biliary tract cancer, brain cancer, breast cancer, cervical cancer, choriocarcinoma, brain or central nervous system (CNS) cancer, colon cancer, connective tissue cancer, endometrial cancer, eye cancer, gastric cancer, intraepithelial neoplasms, esophageal cancer, eye cancer larynx cancer, lymphomas, Hodgkin's lymphoma, liver cancer, lung cancer (e.g. small cell and non-small cell), melanoma, neuroblastoma, oral cavity cancer, ovarian cancer, pancreas cancer, prostate cancer, rectal cancer, sarcomas, thyroid cancer, bone cancer, skin cancer, testicular cancer and/or renal cancer (claimed).

Dwg.0/12

L19 ANSWER 9 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2000-679539 [66] WPIDS
DNC C2000-206683
TI Low adenosine (A) content antisense oligonucleotides which do not trigger adenosine receptors during metabolism, useful e.g. for treating cancers and respiratory obstructions.
DC B04 D16
IN NYCE, J W; CHEN, E; CHEN, L; FERNANDEZ-DE-CASTRO, J; SAUNDERS, D
PA (NYCE-I) NYCE J W; (UYEC-N) UNIV EAST CAROLINA; (CHEN-I) CHEN E; (CHEN-I) CHEN L; (FERN-I) FERNANDEZ-DE-CASTRO J; (SAUN-I) SAUNDERS D
CYC 86
PI WO 2000062736 A2 20001026 (200066)* EN
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 2000040317 A 20001102 (200107)
BR 2000006019 A 20010313 (200118)
EP 1168919 A2 20020109 (200205) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
US 2001053037 A1 20011220 (200206)
MX 2000012093 A1 20010501 (200227)
CN 1330513 A 20020109 (200229)

KR 2002095600 A 20021228 (200330)
JP 2003515525 W 20030507 (200331)

ADT WO 2000062736 A2 WO 2000-US8020 20000324; AU 2000040317 A AU 2000-40317 20000324; BR 2000006019 A BR 2000-6019 20000324, WO 2000-US8020 20000324; EP 1168919 A2 EP 2000-919668 20000324, WO 2000-US8020 20000324; US 2001053037 A1 Provisional US 1999-127958P 19990406, US 2001-902988 20010711; MX 2000012093 A1 MX 2000-12093 20001206; CN 1330513 A CN 2000-801046 20000324; KR 2002095600 A KR 2000-713847 20001206; JP 2003515525 W JP 2000-611873 20000324, WO 2000-US8020 20000324

FDT AU 2000040317 A Based on WO 2000062736; BR 2000006019 A Based on WO 2000062736; EP 1168919 A2 Based on WO 2000062736; JP 2003515525 W Based on WO 2000062736

PRAI US 1999-127958P 19990406; US 2001-902988 20010711

AB WO 200062736 A UPAB: 20001219

NOVELTY - Low adenosine (A) content antisense oligonucleotides (oligo(s)) and compositions (I) comprising them, are new. In the oligo(s), the A is replaced by a 'Universal' or alternative base.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a pharmaceutical composition (I), comprising an oligonucleotide(s) (oligo(s)) which is (are) effective for alleviating bronchoconstriction and/or lung inflammation, **allergy**(ies), or surfactant depletion or hyposecretion, when administered to a mammal (the oligo comprises 0-15% adenosine (A) and is antisense to a target selected from the initiation codon, the coding region, the 5'-end and the 3'-end genomic flanking regions, the 5' and 3' intron-exon junctions, and regions within 2 to 10 nucleotides of the junctions of a gene encoding a target polypeptide associated with lung airway dysfunction or anti-sense to the polypeptide mRNA), combinations of the oligos and/or mixtures of the oligos;

(2) a cell, carrying the oligo(s) of (1);

(3) a kit (II), comprising a delivery device, (in a separate container(s)) the oligo(s) of (I) and instructions for adding a carrier and for use of the kit;

(4) an in vivo method of delivering an anti-sense oligonucleotide(s) (oligo(s)) to one or more target polynucleotide(s), comprising administering into the respiratory system of a subject one or more oligo(s) that are anti-sense to the polynucleotide(s), in an amount effective to reach and hybridize to the target polynucleotide(s), and reduce the production or availability, or to increase the degradation, of the target mRNA, or to reduce the amount of the target polypeptide present in the lungs; and

(5) an in vivo method (III) of delivering an anti-sense oligonucleotide (oligo) to a target polynucleotide associated with bronchoconstriction and/or lung inflammation, **allergy**(ies) and/or surfactant hypoproduction, comprising administering to a subject the composition (I), which comprises an amount of the oligo(s) effective to reach and hybridize to the target polynucleotide(s), and reduce or inhibit the polynucleotide(s)' transcription and/or expression and, therefore, alleviating the bronchoconstriction and/or lung inflammation, **allergy**(ies) and/or surfactant hypoproduction.

ACTIVITY - Respiratory; bronchodilator; antiinflammatory; immunosuppressive; antiasthmatic; analgesic; hypotensive; cytostatic.

MECHANISM OF ACTION - Antisense inhibition of nucleic acid/protein expression.

USE - The oligo(s) may be formulated into compositions (I) and used (III) to down-regulate the expression and or activity of target polypeptides associated with lung/respiratory disorders (especially) and malignancies, such as stimulating and activating peptide factors and transmitters, transcription factors, immunoglobulins and antibodies, antibody receptors, cytokines and chemokines, endogenously produced specific and non-specific enzymes, binding proteins, adhesion molecules and their receptors, cytokine and chemokine receptors, adenosine

receptors, bradykinin receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, defensins, growth factors, vasoactive peptides and receptors, binding proteins and malignancy associated proteins (specific target polypeptides given in the specification or the TECHNOLOGY FOCUS section of abstract). The oligos may be used in this way to treat disorders including respiratory obstruction (especially pulmonary obstruction and/or bronchoconstriction) and/or lung inflammation, **allergy**(ies) and/or surfactant hypoproduction which are associated with a disease or condition selected from pulmonary vasoconstriction, inflammation, allergies, **asthma**, impeded respiration, respiratory distress syndrome (RDS), pain, cystic fibrosis (CF), allergic rhynitis (AR), pulmonary hypertension, emphysema, chronic obstructive pulmonary disease (COPD), pulmonary transplantation rejection, pulmonary infections, bronchitis, and/or cancer (claimed).

ADVANTAGE - The oligo(s) are free of adenosine (A), or have a low A content, this minimizes triggering of adenosine receptors during metabolism. The oligo(s) may be administered in combination with other therapeutic agents.

Two hyper sensitive monkeys (ascaris sensitive) were challenged with inhaled adenosine with and without pretreatment with an antisense oligo (comprising GATGGAGGGCGGCATGGCGGG). The PC40 adenosine was calculated from the data as being equivalent to the amount of adenosine in mg that causes a 40% decrease in dynamic compliance in hyper-sensitive airways. The oligo was administered at 10 mg/day for 2 days by inhalation. On the third day, the PC40 adenosine was measured again. The PC40 value prior to the treatment with the oligo was compared to the PC40 adenosine taken after administration of the oligo. The results indicated showed that any sensitivity to adenosine was completely eliminated by administration of the oligo.

Dwg.0/0

L19 ANSWER 10 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2000-572150 [53] WPIDS
DNC C2000-170608
TI Determining the existence of a correlation between the pathology of a disease and a gene or mRNA encoding a target polypeptide suspected of being associated with the disease.
DC B04 D16
IN NYCE, J W
PA (EPIG-N) EPIGENESIS PHARM INC
CYC 88
PI WO 2000051621 A1 20000908 (200053)* EN 53p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 2000035123 A 20000921 (200065)
BR 2000009247 A 20011120 (200202)
EP 1165093 A1 20020102 (200209) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CN 1348376 A 20020508 (200253)
JP 2002537792 W 20021112 (200275) 104p
KR 2002068262 A 20020827 (200309)
ADT WO 2000051621 A1 WO 2000-US5643 20000302; AU 2000035123 A AU 2000-35123 20000302; BR 2000009247 A BR 2000-9247 20000302, WO 2000-US5643 20000302; EP 1165093 A1 EP 2000-913730 20000302, WO 2000-US5643 20000302; CN 1348376 A CN 2000-806759 20000302; JP 2002537792 W JP 2000-602288 20000302, WO 2000-US5643 20000302; KR 2002068262 A KR 2001-711238 20010903
FDT AU 2000035123 A Based on WO 2000051621; BR 2000009247 A Based on WO

2000051621; EP 1165093 A1 Based on WO 2000051621; JP 2002537792 W Based on WO 2000051621

PRAI US 1999-122950P 19990305

AB WO 200051621 A UPAB: 20001023

NOVELTY - A method for determining the existence of a correlation between the pathology of a disease or condition and a gene or mRNA encoding a target polypeptide suspected of being associated with a disease or condition, is new.

DETAILED DESCRIPTION - A method of determining the existence of a correlation between the function of a disease or condition and a gene or mRNA encoding a target polypeptide suspected of being associated with a disease or condition. The method comprises:

(1) obtaining oligonucleotides (oligos) consisting of up to about 15% adenosine (A) and which is anti-sense to a target selected from target genes and their corresponding mRNAs, genomic and mRNA flanking regions selected from 3' and 5' intron-exon borders and the juxta-section between coding and non-coding regions and all mRNA segments encoding polypeptides associated with a pre-selected disease or condition;

(2) selecting an oligo that significantly inhibits or ablates expression of the polypeptide encoded by the mRNA on in vitro hybridization to the target mRNA;

(3) administering the selected oligo to a subject for in vivo hybridization to the target mRNA; and

(4) and assessing the subject's function that is associated with the disease or condition before and after administration of the oligo (a change in the function's value greater than about 70% indicates a positive correlation, about 40-70% a possible correlation and below about 30% a lack of correlation).

USE - The anti-sense oligo is administered to the lung, brain, heart, kidney, tumor, blood, skin, eye, scalp, nose panages, testes, cervix, oral cavity, pharynx, eophagus, small or large intestine, synovial tissue, muscle tissue, ovaries, ear canal or in vitro. The disease or condition afflicts the lung, brain, heart, kidney, tumor, blood, immune system, skin, eye, scalp, nose panages, testes, cervix, oral cavity, pharynx, eophagus, small or large intestine, synovial tissue, muscle tissue, ovaries and ear canal. The disease or condition is particularly one which afflicts the lung (particularly being associated with bronchoconstriction, lung inflammation and/or **allergy**(ies)), afflicts the brain or is associated with brain activity, is associated with immune dysfunction (particularly where the target is selected from immunoglobulins, antibody receptors, cytokines, cytokine receptors, gene(s) and the corresponding mRNA(s) encoding them, the genes and mRNA flanking regions and intron and exon borders), afflicts the cardiovascular system, associated with the gastrointestinal system or is associated with a malignancy or cancer (particularly where the target is selected from immunoglobulins and antibody receptors, gene(s) and mRNA(s) encoding them, genes and mRNAs associated with oncogenes and genomic and mRNA flanking regions and intron and exon borders). The target gene is selected from genes and mRNAs encoding polypeptides selected from transcription factors, stimulating and activating factors, cytokines and their receptors, interleukins, interleukin receptors, chemokines, chemokine receptors, endogenously produced specific and non-specific enzymes, immunoglobulins, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters and their receptors, adhesion molecules, defensines, growth factors, vasoactive peptides and their receptors, peptide receptors and binding proteins and target genes and mRNAs corresponding to oncogenes and their flanking regions and intron and exon borders. The encoded polypeptides are selected from NfkappaB Transcription Factor, Interleukin-8 Receptor (IL-8 R), Interleukin-5 Receptor (IL-5 R), Interleukin-4 Receptor (IL-4 R), Interleukin-3 Receptor (IL-3 R), Interleukin-1beta (IL-1beta), Interleukin-1beta Receptor (IL-1beta R), Eotaxin, Tryptase, Major Basic Protein, beta2-adrenergic Receptor Kinase,

Endothelin Receptor A, Endothelin Receptor B, Preproendothelin, Bradykinin B2 Receptor, IgE High Affinity Receptor, Interleukin 1 (IL-1), Interleukin 1 Receptor (IL-1 R), Interleukin 9 (IL-9), Interleukin 9 Receptor (IL-9 R), Interleukin 11 (IL-11), Interleukin 11 Receptor (IL-11 R), Inducible Nitric Oxide Synthase, Cyclooxygenase (COX), Intracellular Adhesion Molecule 1 (ICAM-1) Vascular Cellular Adhesion Molecule (VCAM), Rantes, Endothelial Leukocyte Adhesion Molecule (ELAM-1), Monocyte Activating Factor, Neutrophil Chemotactic Factor, Neutrophil Elastase, Defensin 1, 2 and 3, Muscarinic Acetylcholine Receptors, Platelet Activating Factor, Tumor Necrosis Factor alpha, 5-lipoxygenase, Phosphodiesterase IV), Substance P, Substance P Receptor, Histamine Receptor, Chymase, CCR-1 CC Chemokine Receptor, CCR-2 CC Chemokine Receptor, CCR-3 CC Chemokine Receptor, CCR-4 CC Chemokine Receptor, CCR-5 CC Chemokine Receptor, Prostanoid Receptors, GATA-3 Transcription Factor, Neutrophil Adherence Receptor, MAP Kinase, Interleukin-9 (IL-9), NFAT Transcription Factors, STAT 4, MIP-1alpha, MCP-2, MCP-3, MCP-4, Cyclophillins, Phospholipase A2, Basic Fibroblast Growth Factor, Metalloproteinase, CSBP/p38 MAP Kinase, Tryptose Receptor, PDG2, Interleukin-3 (IL-3), Interleukin-1beta (IL-1beta), Cyclosporin A-Binding Protein, FK5-Binding Protein, alpha4etal Selectin, Fibronectin, alpha4beta7 Selectin, Mad CAM-1, LFA-1 (CD11a/CD18), PECAM-1, LFA-1, Selectin, C3bi, PSGL-1, E-Selectin, P-Selectin, CD-34, L-Selectin, p150,95, Mac-1 (CD11b/CD18), Fucosyl transferase, VLA-4, CD-18/CD11a, CD11b/CD18, ICAM2 and ICAM3, C5a, CCR3 (Eotaxin Receptor), CCR1, CCR2, CCR4, CCR5, LTB-4, Ap-1 Transcription Factor, Protein kinase C, Cysteinyl Leukotriene Receptor, Tachychinnen Receptors (tach R), IkappaB Kinase 1 and 2, STAT 6, c-mas and NF-Interleukin-6 (NF-IL-6) and their flanking regions and intron and exon borders.

Dwg.0/4

L19 ANSWER 11 OF 16 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AN 2003-19992 BIOTECHDS
TI Treating non-allergic inflammatory diseases, such as psoriasis, eczema, allergic contact dermatitis, latex dermatitis or inflammatory bowel disease by administering an immunostimulatory nucleic acid; involving vector-mediated gene transfer and expression in host cell for use in gene therapy, recombinant vaccine and nucleic acid vaccine preparation
AU KRIEG A M; BERG D J
PA KRIEG A M; BERG D J
PI US 2003050268 13 Mar 2003
AI US 2002-112653 29 Mar 2002
PRAI US 2002-112653 29 Mar 2002; US 2001-279642 29 Mar 2001
DT Patent
LA English
OS WPI: 2003-521815 [49]
AB DERWENT ABSTRACT:

NOVELTY - Treating non-allergic inflammatory disease comprises administering to a subject having or at risk of developing a non-allergic inflammatory disease an immunostimulatory nucleic acid for prevention or treatment of the disease.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) treating inflammatory bowel disease; (2) a pharmaceutical composition; and (3) augmenting Th-1 like immune activation induced by the immunostimulatory nucleic acid.

BIOTECHNOLOGY - Preferred Method: Treating non-allergic inflammatory disease further comprises administering an anti-inflammatory agent comprising corticosteroids, nonsteroidal anti-inflammatory drugs, vitamin A or D analogs, retinoids, cytokines or cytokine receptors, or their agonists or antagonists, antibodies specific for cytokines or cytokine receptors or immunosuppressive agents. The immunostimulatory nucleic acid reduces or prevents non-allergic inflammation in a tissue of the subject. It induces IL-12, IFN-alpha, IFN-gamma or IL-10. It comprises at least

one stabilized internucleotide linkage, which is a **phosphorothioate** linkage. It has a backbone completely made up of stabilized internucleotide linkages. It is a **CpG**, T-rich, poly-G or synthetic nucleic acid. It comprises 6-100 or 8-40 bp. The poly-G nucleic acid comprises the formula 5'-X1X2GGGX3X4-3'. X1,X2,X3 or X4 = any nucleotide other than G. The immunostimulatory nucleic acid is administered locally to intact epithelium or systemically. The non-allergic inflammatory disease involves a mucosal epithelium. It comprises psoriasis, eczema, allergic contact dermatitis, latex dermatitis or inflammatory bowel disease. Treating inflammatory bowel disease comprises administering to a subject having or at risk of developing an inflammatory bowel disease the immunostimulatory nucleic acid for prevention or treatment of the disease. The inflammatory bowel disease is ulcerative colitis or Crohn's disease. Augmenting Th-1 like immune activation induced by the immunostimulatory nucleic acid comprises: (1) contacting an immune cell with the immunostimulatory nucleic acid to induce Th-1 like immune activation; and (2) contacting the immune cell with an inhibitor of cyclooxygenase-2 (COX-2) expression. The COX-2 inhibitor is NSAID. The method may also comprise contacting the immune cell with an agent that inhibits PGE2 signaling through its receptor. Preferred Composition: The pharmaceutical composition comprises: (1) the immunostimulatory nucleic acid; (2) a non-allergic inflammatory disease medicament; and (3) a carrier. The carrier is a lotion, cream, ointment or gel.

ACTIVITY - Antiinflammatory; Dermatological; Antipsoriatic; Antiulcer. No biological data given.

MECHANISM OF ACTION - Gene therapy; Vaccine.

USE - The method is useful for treating non-allergic inflammatory diseases, such as psoriasis, eczema, allergic contact dermatitis, latex dermatitis or inflammatory bowel disease e.g., ulcerative colitis or Crohn's disease (claimed).

ADMINISTRATION - Dosage comprises 0.1 microg to 10000 mg, preferably 10 microg to 8000 mg per kg body weight. The pharmaceutical composition is administered via oral, topical, parenteral or transdermal route (claimed). (240 pages)

L19 ANSWER 12 OF 16 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
AN 2003-12819 BIOTECHDS
TI Treatment of a subject having, or at risk of developing cancer, involves the use of an immunostimulatory nucleic acid having a modified backbone in combination with a cancer medicament;
phosphorothioate-modified backbone poly-G nucleic acid transfer and expression in host cell for immunostimulant and gene therapy
AU BRATZLER R L; PETERSEN D M
PA BRATZLER R L; PETERSEN D M
PI US 2002156033 24 Oct 2002
AI US 2001-800266 5 Mar 2001
PRAI US 2001-800266 5 Mar 2001; US 2000-187214 3 Mar 2000
DT Patent
LA English
OS WPI: 2003-275279 [27]
AB DERWENT ABSTRACT:
NOVELTY - Treatment (T1) of a subject having cancer involves administering an immunostimulatory nucleic acid (1) having modified backbone and a cancer medicament (M1) selected from chemotherapeutic agent, immunotherapeutic agent, cancer vaccine or hormone therapy. The poly-G nucleic acid is not conjugated to (M1) and is free of **CpG** and T-rich motif.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) Treatment (T3) of a subject having or at risk of developing cancer involving administering an immunostimulatory nucleic acid selected from **CpG** nucleic acid or a non-**CpG** nucleic acid (where the

nucleic acid has a **phosphorothioate** modified backbone) and a cancer medicament such as hormone therapy (HT); and (2) A device for delivering immunostimulatory nucleic acid to a subject receiving an intravenous injection, comprising an intravenous device (D1) selected from a bag or a tube and the nucleic acid, where the nucleic acid is coated on an internal surface of (D1) or is embedded within (D1).

ACTIVITY - Cytostatic; Fungicide; Antibacterial; Antiparasitic; Virucide; Antiallergic; Antianemic; Hemostatic.

MECHANISM OF ACTION - Cell growth inhibitor.

USE - The composition is for the treatment of cancer (e.g. bone cancer, brain and CNS cancer, connective tissue cancer, esophageal cancer, eye cancer, Hodgkin's lymphoma, larynx cancer, oral cavity cancer, skin cancer, and testicular cancer), and for preventing allergic responses in those receiving blood transfusions (all claimed). It is also useful for the treatment of fungal, bacterial, parasitic and viral infections.

ADMINISTRATION - Administration is oral, parenteral (including intramuscular or intravenous), intranasal, intratracheal, through inhalation, ocular, vaginal, buccal or rectal. No dosage given.

ADVANTAGE - The combination of the immunostimulatory nucleic acids and the cancer medicament is synergistic. The combination allows for the administration of higher doses of cancer medicaments without as many side effects, and allows for the administration of lower, sub-therapeutic doses of either compound, but with higher efficacy than would otherwise be achieved using such low doses. The immunostimulatory nucleic acids function by enhancement of anti-body dependent cell cytotoxicity. This mechanism provides long lasting effects of nucleic acids, thus reducing dosing regimens, improving compliance and maintenance therapy, reducing emergency situations and improving quality of life. (32 pages)

L19 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:570637 CAPLUS
DN 139:132442
TI Methods and products for enhancing immune responses using imidazoquinoline compounds in combination with modified immunostimulatory oligonucleotide
IN Krieg, Arthur M.; Schetter, Christian; Bratzler, Robert L.; Vollmer, Jorg; Jurk, Marion; Bauer, Stefan
PA University of Iowa Research Foundation, USA
SO U.S. Pat. Appl. Publ., 112 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003139364	A1	20030724	US 2002-272502	20021015
PRAI	US 2001-329208P	P	20011012		

AB The invention involves administration of an imidazoquinoline agent in combination with another therapeutic agent. The combination of drugs may be administered in synergistic amts. or in various dosages or at various time schedules. The invention also relates to kits and compns. concerning the combination of drugs. The combinations can be used to enhance ADCC, stimulate immune responses and/or patient and treat certain disorders. Specifically, the imidazoquinoline compns. R-848 is used which is shown to be more potent inducer of proinflammatory cytokines NF-.kappa.B in 293T cells by reconstitution of TLR9 signaling through co-transfecting TLR9, TLR8 and TLR7 into 293T cell. Furthermore, **CpG** oligonucleotides (ODNs, in particular, **CpG** ODN #7909) and R-848 are tested either together or individually for their ability to augment a cytolytic T lymphocyte response against antigen (e.g., HBsAg) in vivo using mouse model. The combination of R-848 and **CpG** ODN together is shown to result in an additive effect; while no augmentation of the CTL response over antigen alone is obsd. using control ODN either alone or with R-848.

The distribution of antibody isotype also shows **CpG** ODN produces higher levels of IgG2a antibodies regardless of whether R-848 is present, and R-848 appears to increase the level of IgG2a and decrease the level of IgG1 as compared to the antigen alone response.

L19 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:154198 CAPLUS
DN 138:203655
TI Oligonucleotides containing stimulatory **phosphorothioate** motif and neutralizing motif for treating infections, allergies and cancers
IN Krieg, Arthur M.; Vollmer, Jorg; Ulhman, Eugen
PA Coley Pharmaceutical Group, Inc., USA; Coley Pharmaceutical G.m.b.H.; University of Iowa Research Foundation
SO PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003015711	A2	20030227	WO 2002-US26468	20020819
WO 2003015711	C2	20030410		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003148976	A1	20030807	US 2002-224523	20020819
PRAI US 2001-313273P	P	20010817		
US 2002-393952P	P	20020703		

AB A class of immunostimulatory nucleic acids having at least two functionally and structurally defined domains is provided. The nucleic acids or oligodeoxynucleotides contg. a combination of a stimulating motif (i.e. **CpG**) and a neutralizing motif (i.e. CG-rich palindrome or CG repeats) are, surprisingly, highly immunostimulatory. This class of combination motif immunostimulatory nucleic acids characteristically activate B cells and NK cells, and also induce prodn. of type I interferon. The immunostimulatory nucleic acids or oligonucleotides are therefore, useful for treating a variety of immune related disorders such as cancer, infectious disease, and allergic disorders.

L19 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:736889 CAPLUS
DN 137:273194
TI Modulation of immunostimulatory activity of immunostimulatory oligonucleotide analogs by positional chemical changes
IN Kandimalla, Ekambar R.; Zhao, Qiuyan; Yu, Dong; Agrawal, Sudhir
PA USA
SO U.S. Pat. Appl. Publ., 41 pp., Cont.-in-part of U.S. Ser. No. 712,898.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2002137714	A1	20020926	US 2001-965116	20010926
PRAI US 2000-235452P	P	20000926		
US 2000-235453P	P	20000926		

US 2000-712898 A2 20001115
OS MARPAT 137:273194
AB The invention relates to the therapeutic use of oligonucleotides or oligonucleotide analogs as immunostimulatory agents in immunotherapy applications. The invention provides methods for enhancing the immune response caused by immunostimulatory oligonucleotide compds. A study of the structure-activity relationships of modified **CpG** oligodeoxynucleotide phosphorothioates was made.

L19 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:463662 CAPLUS
DN 137:293467
TI **Phosphorothioate** oligonucleotides: looking for the motif(s) possessing immunostimulatory activities in humans
AU Brugnolo, Francesca; Annunziato, Francesco; Sampognaro, Salvatore; Manuelli, Cinzia; Cosmi, Lorenzo; Romagnani, Sergio; Maggi, Enrico; Parronchi, Paola
CS Department of Internal Medicine, University of Florence, Florence, Italy
SO Advances in Experimental Medicine and Biology (2001), 495(Progress in Basic and Clinical Immunology), 261-264
CODEN: AEMBAP; ISSN: 0065-2598
PB Kluwer Academic/Plenum Publishers
DT Journal
LA English
AB **Phosphorothioate** oligonucleotides (PS-ODNs) showed various effects on human cells, inducing B cell proliferation and prodn. of cytokines from cells of innate immunity. PS-ODNs also shifted the functional profile of allergen-specific T cells from a prevalent Th2 towards a prevalent Th1-like phenotype. These effects were independent of the absence or presence of classic **CpG** motifs, indicating that immunostimulatory sequences active in humans are different from those described in mice. PS-ODNs in which **CpG** dinucleotides were inverted into GpC still retained a significant effect on B and T cells.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 07:59:41 ON 17 SEP 2003)

FILE 'BIOSIS, MEDLINE, AGRICOLA, EMBASE, CABA, WPIDS, JAPIO, BIOTECHDS, LIFESCI, CAPLUS' ENTERED AT 08:01:24 ON 17 SEP 2003
E BRATZLER ROBERT L/AU
L1 41 S E1-E3
E PETERSEN DEANNA M/AU
L2 7 S E3
E FOURON YVES/AU
L3 31 S E1-E3
L4 73 S L1-L3
L5 5 S L4 AND (ASTHMA OR ALLERGIC OR ALLERGY)
L6 4 S L5 AND CPG
L7 27 S L4 AND (CPG OR IMMUNOSTIMULATORY OR NUCLEIC ACID)
L8 11 DUP REM L7 (16 DUPLICATES REMOVED)
L9 418622 S ASTHMA OR ALLERGY
L10 29905 S CPG OR NUCLEIC ACID (5A) ADJUVANT
L11 1292 S L9 AND (REFRACTORY OR HYPORESPONSIVE OR HYPO-RESPONSIVE OR N
L12 785 DUP REM L11 (507 DUPLICATES REMOVED)
L13 523 S L9 AND L10
L14 285 DUP REM L13 (238 DUPLICATES REMOVED)
L15 1 S L12 AND L14
L16 285 S L13 AND L14
L17 161 S L16 AND ASTHMA

```
L18          163 S L16 AND ALLERGY
L19           16 S L18 AND PHOSPHOROTHIOATE

=> s l17 and phosphorotioate
L20           0 L17 AND PHOSPHOROTIOATE

=> s l17 and modified backbone
L21           1 L17 AND MODIFIED BACKBONE

=> d bib ab

L21  ANSWER 1 OF 1  WPIDS  COPYRIGHT 2003 THOMSON DERWENT on STN
AN   2002-723213 [78]   WPIDS
DNC  C2002-204705
TI   New compositions comprising CpG-like immunostimulatory nucleic
     acids, useful for treating or preventing infectious diseases, cancer,
     allergy, asthma, immunodeficiency, anemia,
     thrombocytopenia or neutropenia.
DC   B04 C06 D16
IN   SCHETTER, C; VOLLMER, J
PA   (COLE-N) COLEY PHARM GROUP LTD
CYC  100
PI   WO 2002069369 A2 20020906 (200278)* EN  148p
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
            NL OA PT SD SE SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
            KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
            RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM
            ZW
ADT  WO 2002069369 A2 WO 2001-IB2888 20011210
PRAI US 2000-254341P  20001208
AB   WO 200269369 A UPAB: 20021204
     NOVELTY - Compositions, which comprise a pharmaceutical carrier and an
     immunostimulatory nucleic acid having a sequence including at least the
     formula (I), (II) or (III), are new.
          DETAILED DESCRIPTION - Compositions comprising an immunostimulatory
     nucleic acid having a sequence, including at least any one of the
     following formulae, are new.
          5' X1X2CGX3X4 3' (I) 5' X1X2ZYX3X4 3' (II) 5' X1X2C1GX3X4 3' (III).
     C = methylated;
          Y = inosine, 2-aminopurine, xanthosine, N7-methyl-xanthosine,
     nebularine or dSpacer;
          Z = cytosine, 2'-deoxyuridine (dU), 5-fluoro-2'-dU or dSpacer, and
     where Z is not cytosine when Y is inosine;
     C1 = cytosine;
          I = inosine; and
          X1, X2, X3 and X4 = nucleotides.
          An INDEPENDENT CLAIM is also included for a method for inducing an
     immune response by administering to a subject the novel composition.
          ACTIVITY - Antimicrobial; Cytostatic; Antiallergic; Antiasthmatic;
     Immunostimulant; Antianemic; Hemostatic.
          MECHANISM OF ACTION - Interleukin-Inducer-1-Beta;
     Interleukin-Inducer-2; Interleukin-Inducer-6; Interleukin-Inducer-12;
     Interleukin-Inducer-18; TNF-Inducer-Alpha; Interferon-Inducer-Alpha;
     Interferon-Inducer-Gamma.
          Peripheral blood monocytes (PBMC) (3 multiply 106 cells/ml) obtained
     from several blood donors were incubated for 8 hours with 6 micro g/ml of
     the composition containing oligodeoxynucleotide (ODN) 2006, 2117, 2137, or
     1 micro g/ml lipopolysaccharide (LPS) as positive control. Negative
     controls were similarly incubated for 8 hours in the absence of added ODN
     or LPS. After 8 hours, supernatants were collected and IL-1 beta (which
     plays a role in the stimulation of B, T and NK cells, and participates in
```

the conversion of Langerhans cells to professional antigen-presenting dendritic cells, and acts as a chemoattractant for leukocytes) was measured by enzyme linked immunosorbent assay (ELISA). Results showed that **CpG** ODN were potent inducers of IL- beta secretion.

USE - The compositions are useful for inducing an immune response in a subject, e.g. dog, cat, horse, cow, pig, sheep, goat, rabbit, guinea pig, non-human primate, chicken or fish. The compositions are useful for treating or preventing infectious diseases, cancer, **allergy** or **asthma**. The compositions are also useful for enhancing or stimulating bone marrow proliferation in a subject who has or is at risk of developing an immunodeficiency, particularly in a subject undergoing chemotherapy. The compositions are also useful for enhancing erythropoiesis in a subject who has or is at risk of developing anemia, for enhancing thrombopoiesis in a subject who has or is at risk of developing thrombocytopenia, for enhancing neutrophil proliferation in a subject who has or is at risk of developing neutropenia, or for inducing cytokine (e.g. interleukin (IL)-1 beta , IL-2, IL-6, IL-12, IL-18, tumor necrosis factor (TNF)- alpha , interferon (IFN)- alpha or IFN- gamma) production. (All claimed).

Dwg.0/18